DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201532

WRITTEN REQUEST

Eisai, Inc.
Attention: Patricia H. Sass
Manager, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Sass:

Reference is made to your March 22, 2016, Proposed Pediatric Study Request (PPSR) for Halaven (eribulin mesylate).

BACKGROUND

Eribulin mesylate is a microtubule dynamics inhibitor and is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*.

On November 15, 2010, Halaven was approved for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. On January 28, 2016, Halaven was approved for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen based on an improvement on overall survival (OS) compared to dacarbazine.

Soft tissue sarcomas (STS) are a diverse group of malignancies that are generally characterized by tissue of origin and are comprised of over 50 different histologies. Sarcomas represent about 6% of all malignancies in children and adolescents, and 1% in adults, with an annual incidence of 10 in 1 million children under the age of 15 years and 2 to 3 per 100,000 in adults. The most common histological type in childhood is rhabdomyosarcoma (RMS), which accounts for aproximately 39% of all cases of STS. The distribution of STS differs significantly between children and adults and dedicated pediatric clinical trials are needed to evaluate novel therapies. Initial treatment of RMS and Ewing sarcoma (EWS) consists of well-established multi-agent chemotherapy regimens combined with local control with surgery, radiation therapy, or both. Initial treatment for non-rhabdomyosarcoma soft tissue tumors (NRSTS) consists of local control with surgical resection and possibly chemotherapy depending on the subtype. Survival after relapse is poor for all of these histolgies: estimated 5 year survival rates for RMS are 5-24%, median OS for EWS is approximately one year, and for those with NRSTS the outlook is also poor and varies somewhat by histology. New therapies are needed for this patient population and eribulin mesylate was found to be active in a particular type of adult STS and has shown activity in preclinical models of pediatric tumors, including sarcomas.

To obtain needed pediatric information on eribulin mesylate for the treatment of pediatric patients (ages >6 months to <18 years) with relapsed or refractory rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, and Ewing's sarcoma, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below. FDA is not requesting studies in neonates or infants less than 6 months of age as the incidence of soft tissue sarcomas in this age group is very rare and, if diagnosed, the vast majority of patients will be older than 6 months at the time of relapsed or refractory disease.

- ***Nonclinical study(ies)*:**

  Based on review of the available non-clinical toxicology data, no additional animal studies are required at this time to support the clinical studies described in this written request.

- ***Clinical studies:***

  Study 1: A Phase 1 study of eribulin mesylate in children with refractory or recurrent solid tumors (excluding CNS), including lymphomas.

  Study 2: A Phase 1/2 single-arm study evaluating the safety and efficacy of eribulin mesylate in combination with irinotecan in children with refractory or recurrent rhabdomyosarcoma (RMS) and nonrhabdomyosarcoma soft tissue sarcoma (NRSTS).

  - *Part 1:* Patients with relapsed or refractory extracranial solid tumors will receive eribulin mesylate in combination with either weekly or daily irinotecan in limited dose-escalation cohorts in order to define a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of the combination to be evaluated in Part 2.
  - *Part 2:* Patients with relapsed or refractory RMS and NRSTS will receive eribulin mesylate and irinotecan in the dose and schedule chosen for further evaluation in Part 1.

  Study 3: A Phase 2, multicenter, two-arm, randomized, open-label study to assess the efficacy and safety of eribulin mesylate versus a to-be-determined active comparator drug in pediatric patients with relapsed/refractory rhabdomyosarcoma (RMS), nonrhabdomyosarcoma (NRSTS), and Ewing sarcoma (EWS).

FDA requires that protocols for Studies 2 and 3 be submitted to the Agency for review and agreement prior to trial initiation. FDA acknowledges that Study 1 has been previously reviewed and agreed to.

Efficacy in pediatric patients ages 6 months to < 18 years with RMS and EWS cannot be extrapolated and will be determined by the studies outlined in the WR.

- ***Objectives of each study:***

Study 1:

- *Primary:*
  - To determine the MTD and/or RP2D of eribulin mesylate administered as an intravenous (IV) infusion on Day 1 and 8 of a 21-day cycle to pediatric patients with refractory or recurrent solid tumors.
  - To define the toxicities of eribulin mesylate administered on this schedule in pediatric cancer patients.
  - To characterize the pharmacokinetics (PK) of eribulin mesylate in pediatric patients with refractory or recurrent cancer.

- *Secondary:*
  - To preliminarily define the antitumor activity of eribulin mesylate in pediatric patients.
  - To characterize the pharmacokinetics of eribulin mesylate in infants with refractory or recurrent cancer.

Study 2:

- *Primary (Part 1):*
  - To determine the MTD or RP2D of eribulin mesylate in combination with weekly and daily irinotecan hydrochloride in pediatric patients with relapsed/refractory solid tumors.

- *Primary (Part 2):*
  - To assess the overall response rate (ORR) of eribulin mesylate in combination with irinotecan hydrochloride in pediatric patients with relapsed/refractory RMS and NRSTS.

- *Secondary:*
  - To assess the safety and tolerability of eribulin mesylate in combination with irinotecan hydrochloride.
  - To assess the progression free survival (PFS) of patients with RMS or NRSTS treated with eribulin mesylate in combination with irinotecan hydrochloride.
  - To determine the optimal schedule of irinotecan hydrochloride when administered with eribulin mesylate.
  - To assess the clinical benefit rate (CBR) at 12 weeks of eribulin mesylate in combination with irinotecan hydrochloride in pediatric patients defined as the proportion of subjects with complete response (CR), partial response (PR), or stable disease (SD) at week 12 based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
  - To evaluate the pharmacokinetic profile and drug-drug interactions of eribulin mesylate and irinotecan and its active metabolite, when eribulin and irinotecan are co-administered.

Study 3:

- *Primary:*
  - To compare the ORR as measured by RECIST v1.1 in pediatric patients with relapsed/refractory RMS, NRSTS, or EWS treated with eribulin mesylate (Arm A) vs. those treated with a to-be-determined active comparator (Arm B).

  - *Secondary:*
    - To non-comparatively evaluate the ORR and PFS using RECIST v1.1 of Arm A and Arm B in pediatric patients with relapsed/refractory RMS, NRSTS, or EWS.
    - To evaluate the safety and tolerability of both arms of treatment.

- ***Patients to be Studied:***

  Study 1:

  Minimum of 12 patients ages 6 months to less than 18 years of age with refractory or recurrent solid tumors (excluding CNS tumors), including lymphomas.

  Study 2:

  Minimum of 18 patients ages 12 months to <18 years with relapsed or refractory solid tumors (Part 1) and RMS and NRSTS (Part 2).

  Study 3:

  Patients ages 12 months to <18 years with relapsed or refractory RMS, NRSTS and EWS. A sufficient number of patients in a statistically powered trial will be studied in order to preliminarily evaluate the clinical activity of eribulin mesylate as assessed by overall response rate in this patient population.

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- ***Study endpoints:***

  - *Efficacy Endpoints:*

    Study 1:

    - Determine an MTD or RP2D of eribulin mesylate in pediatric patients with relapsed or refractory solid tumors (excluding CNS tumors), including lymphomas.
    - Describe preliminary evidence of antitumor activity of eribulin mesylate in pediatric patients with solid tumors.

Study 2:

- Determine an MTD or RP2D and schedule of eribulin mesylate in combination with irinotecan and describe preliminary evidence of activity of this combination as assessed by ORR in pediatric patients with RMS and NRSTS.

Study 3:

- Determine the clinical activity of eribulin mesylate compared to an active comparator as assessed by RECIST v1.1 by blinded independent radiologic review.

- *Safety Endpoints:*

  Study 1 and 3:

  - Descriptive analyses of adverse events of eribulin mesylate in pediatric patients with refractory solid tumors, including the incidence of adverse events, severe adverse events, serious adverse events, and fatal adverse events. Type, frequency, and severity of laboratory abnormalities will also be analyzed.

  Study 2:

  - Descriptive analyses of adverse events of eribulin mesylate in combination with irinotecan in pediatric patients with refractory solid tumors, including the incidence of adverse events, severe adverse events, serious adverse events, and fatal adverse events. Type, frequency, and severity of laboratory abnormalities will also be analyzed.

- *Pharmacokinetic Endpoints:*

  Pharmacokinetic data appropriately analyzed to obtain relevant PK parameters (e.g. AUC, C_{max}, CL, V_d, etc.) to adequately characterize the PK of eribulin in pediatric patients must be provided from the following minimum numbers of patients from across the entire pediatric development program:

  - 6 patients < 6 years old
  - 10 patients 6 to < 12 years old
  - 10 patients 12 to < 18 years old

  If appropriate, combine data from all studies included in the WR to develop PK models and explore exposure-response relationships for measures of safety and efficacy.

- ***Known Drug Safety concerns and monitoring:***

  - The most common adverse reactions (incidence ≥25%) associated with eribulin are neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. These common adverse reactions will be monitored during protocol-defined visits and laboratory examinations and will be managed with dose-reductions or discontinuations as defined in the protocols and supportive care as appropriate.

- Eribulin has been associated with QT prolongation in adult QT studies. Pediatric patient with baseline QT prolongation (>480msec), including those with congenital long QT syndrome, will be excluded. ECG monitoring will be conducted across the pediatric program pre-study, during Cycle 1, and as clinically indicated.

- ***Extraordinary results:*** In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- ***Drug information:***

  - *Dosage form:* 1.0 mg E7389 drug substance in 2.0 mL of solution. Eribulin mesylate drug product is a clear, colorless, and sterile solution packaged in a glass vial.
  - *Route of administration:* intravenous (IV)
  - *Regimen:*

    Study 1:

    - Limited dose-escalation cohorts of single-agent eribulin IV on days 1 and 8 of 21 day cycles as follows:
      - Dose Level 1 - 1.1 mg/m^2
      - Dose Level 2 - 1.4 mg/m^2
      - Dose Level 3 - 1.8 mg/m^2
      - Dose Level 4 - 2.2 mg/m^2

    Study 2: (in combination with IV irinotecan hydrochloride)

    - *Schedule A*
      - Dose level -1: eribulin mesylate 1.1 mg/m^2 Day 1 and Day 8 with irinotecan hydrochloride 20 mg/m^2 Days 1-5 of a 21-day cycle
      - Dose level 0: eribulin mesylate 1.4 mg/m^2 Day 1 and Day 8 with irinotecan hydrochloride 20 mg/m^2 Days 1-5 of a 21-day cycle
      - Dose level 1: eribulin mesylate 1.4 mg/m^2 Day 1 and Day 8 with irinotecan hydrochloride 40 mg/m^2 Days 1-5 of a 21-day cycle

    - *Schedule B*
      - Dose level -1: eribulin mesylate 1.1 mg/m^2 with 100 mg/m^2 irinotecan hydrochloride Day 1 and Day 8 of a 21-day cycle
      - Dose level 0: eribulin mesylate 1.4 mg/m^2 with 100 mg/m^2 irinotecan hydrochloride Day 1 and Day 8 of a 21-day cycle

- Dose level 1: eribulin mesylate 1.4 mg/m^2 with 125 mg/m^2 irinotecan hydrochloride Day 1 and Day 8 of a 21-day cycle

Study 3:

Eribulin as a single agent with dose regimen to be determined.

- ***Statistical information, including power of study(ies) and statistical assessments:***

Study 1:

Dose-escalation in order to determine an MTD will be conducted using a rolling-six design. Data presented will be descriptive in nature and will include the number of patients with dose limiting toxicities (DLTs), incidence of adverse events, PK, laboratory data and other safety assessments, and tumor response by patient cohort.

Study 2:

Part 1: Dose escalation in order to determine an MTD will be conducted using a 3+3 design for each schedule with an anticipated maximum of 36 patients. If no MTD is determined for either schedule, Schedule B will be evaluated in Part 2 due to convenience of the regimen.

Part 2: A Simon two-stage design will be used for each histology group with up to a total of 50 patients enrolled (25 per group). The following hypothesis will be tested at a one-sided 5% significance level: H_o: $p \leq 30\%$ vs. H_a: $p \geq 55\%$. In the first stage, nine patients will be accrued. If there are two or fewer responses in these nine patients, the trial will be stopped. Otherwise, 16 additional patients will be accrued in the second stage for a total of 25 patients. The null hypothesis will be rejected if 12 or more responses are observed in 25 patients. This design yields a type I error rate of 0.05 (one-sided) and power of 80% when the true response rate is 55%.

Study 3:

Patients will be randomized (1:1) to either eribulin mesylate (Arm A) or a to-be-determined active comparator (Arm B). The primary endpoint of the study is the comparison of ORR as assessed by RECIST v1.1 by independent review. The hypothesis to be tested and methodology will be determined upon selection of the active comparator.

- ***Labeling that may result from the study(ies)*:** You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that eribulin mesylate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- ***Format and types of reports to be submitted*:** You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- ***Timeframe for submitting reports of the study(ies):*** Reports of the above studies must be submitted to the Agency on or before December 31, 2023.

  Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- ***Response to Written Request:*** Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GREGORY H REAMAN
07/08/2016