Labeling Supplement – Clinical Review
Division of Oncology 3

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Division/Office	DO3/OOD
Medical Officer	Jamie Brewer, MD
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Signatory	Steven Lemery, MD
Product: Established Name (Trade Name)	Eribulin mesylate (HALAVEN)
Formulation	Injection
Established Pharmacologic Class (EPC)	Microtubule inhibitor
Applicant	Eisai, Inc
Recommended Regulatory Action	Approval

1. Executive Summary

This New Drug Application (NDA) Prior Approval Supplement (PAS) is submitted per the requirements of the Pediatric Written Request – Amendment 3 dated November 10, 2021. This supplemental NDA contains results from the following studies:

- Study 1 (E7389-A001-113), a Phase 1 open-label, dose escalation study designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) and to characterize the toxicity and pharmacokinetics of eribulin mesylate
- Study 2 (E7389-G000-213), an open-label, single-arm, multicenter, Phase 1/2 study of eribulin mesylate in combination with weekly and daily irinotecan hydrochloride in children with refractory or recurrent solid tumors
- Study 3 (E7389-G000-223), an open-label, single-arm, multicenter, Phase 2 study designed to assess objective response via investigator assessment in pediatric patients with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS) treated with eribulin mesylate.

In addition, the PAS provides updates to Section 8.4 of the Prescribing Information (PI) to include information regarding the pharmacokinetics observed in the pediatric studies and a request for Pediatric Exclusivity for eribulin mesylate.

The PAS was reviewed by the clinical pharmacology review team. Please refer to the Clinical Pharmacology review memo for additional details

HALAVEN is a microtubule inhibitor 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.
- Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

2. Regulatory Background

On November 15, 2010, FDA granted an approval for NDA 201532 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, eribulin was approved for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

A Proposed Pediatric Study Request (PPSR) for eribulin mesylate was submitted on March 22, 2016, to study patients between ≥12 months to <18 years of age with relapsed or refractory pediatric solid tumors including advanced rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma and Ewing's sarcoma. The original Written Request was issued on July 8, 2016, and included a proposal to conduct four studies, a single-agent dose escalation (Study 1, E7389-A001-113), a combination dose escalation, dose expansion with irinotecan (Study 2, E7389-G000-213), a confirmatory study of single-agent eribulin mesylate in selected tumor types (Study 3, E7389-G000-223) and confirmatory study of the efficacy of eribulin mesylate in combination with irinotecan (Study 4).

On July 26, 2017, Amendment #1 was issued that included revisions to modify Study 2 (E7389-G000-213) to include patients with EWS, to modify Study 3 (E7389-G000-223) from a randomized trial with an active comparator to a single-arm trial, and to modify the design of Study 4 to make initiation of study dependent on the results of Studies 2 and 3. Study 3 was also modified to specify that up to 10 patients in the pre-specified histologic groups (RMS, NRSTS, and EWS) would be enrolled and treated with eribulin mesylate.

On September 11, 2020, Amendment #2 was issued that included revisions to conduct further investigation of eribulin mesylate as a monotherapy in both Studies 3 and 4 and provided specific criteria for Study 4 to be initiated/conducted based solely on the results of a futility analysis in Study 2 rather than based on responses observed in Studies 2 and 3. Additional changes included increasing the upper age limit to 25 years for the pediatric patients in the ongoing studies (Study 2 and Study 3), provided that no more than 25% of patients will be between the ages of 18 to 25 years old.

On November 10, 2021, Amendment #3 was issued that included revisions to remove Study 4 based on the results of the futility analysis in Study 2 (E7389-G000-213). This change was supported by the lack of objective responses observed in any cohort in Study 3 (E7389-G000-223).

3. Review of Clinical Data

Study 1 (E7389-A001-113) was a Phase 1 open-label, dose escalation study designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) and to characterize the toxicity and pharmacokinetics of eribulin mesylate. Patients were enrolled to either Part A1 (≥12 months to <18 years cohort) or Part A2 (>6 months to <12 months cohort). The starting dose for the study was 1.1 mg/m^2 which is approximately 80% of the adult MTD. One subject experienced 2 DLTs (neutropenia and

fatigue) at the 1.4 mg/m2 dose level (n=6). Two patients experienced 1 DLT (neutropenia and neutrophil count decreased) and the 1.8 mg/m^2 dose was assessed to be not tolerable (Dose Level 3, n=5). Since the DLTs observed at the 1.4 mg/m^2 dose level were different classes of events this dose level was expanded to 12 patients and considered to be tolerable. Eribulin administered at 1.4 mg/m^2 on Day 1 and Day 8 during a 21-day cycle was determined to be the MTD. Eribulin exposure increased proportionally with the dose given over the dose range evaluated in this study. There was no evidence of meaningful anti-tumor activity (1 partial response (PR) in 22 treated patients) in pediatric patients with refractory or recurrent solid tumors (excluding CNS) or lymphomas treated with eribulin.

Study 2 (E7389-G000-213) was an open-label, single-arm, multicenter, Phase 1/2 study of eribulin mesylate in combination with weekly and daily irinotecan hydrochloride in children with refractory or recurrent solid tumors. The primary endpoint of the Phase 1 portion of the trial was to determine the MTD or RP2D of the combination in pediatric patients with relapsed/refractory solid tumors, excluding central nervous system (CNS) tumors. Secondary objectives of the Phase 1 portion of the study include an assessment of safety and tolerability and determination of the optimal administration schedule of irinotecan hydrochloride when administered with standard schedule (Days 1 and 8) of eribulin mesylate. The Phase 2 portion of the study was designed to assess the objective response rate (ORR) and duration of response (DOR) of the combination regimen in pediatric patients with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS). Secondary objectives for the Phase 2 portion included an assessment of progression-free survival (PFS) and clinical benefit rate (CBR) at 12 weeks. The study also characterized the pharmacokinetic profile of eribulin mesylate in combination with irinotecan hydrochloride in pediatric patients. None of the 13 patients enrolled to the Phase 1 portion of the study in either dosing scheduled experienced any DLTs. After independent expert recommendations and consultation with the study investigators, the RP2D of the combination regimen was identified as the MTD for Schedule A, eribulin 1.4 mg/m^2 with irinotecan 40 mg/m^2. Although an efficacy evaluation was not an objective of the Phase 1 portion, 2 of the 13 treated patients had confirmed PR. Of the 27 patients (9 patients in each of the RMS, NRSTS, and EWS cohorts) enrolled and treated in the Phase 2 portion at the RP2D, 3 patients had a confirmed investigator-assessed PR (1 patient in each of the RMS, NRSTS, and EWS histology cohorts). The ORR was 11.1% with a duration of response for each responder of 2.86 months (RMS), 1.41 months (NRSTS), and 15.38 months (EWS). The study was stopped based on a futility analysis performed in the first 9 patients in each tumor cohort as there were fewer than the prespecified 3 confirmed responses in any single histologic cohort. The PK parameters of eribulin appeared similar to the values reported from previous clinical experience at the 1.4 mg/m^2 dose.

Study 3 (E7389-G000-223) was an open-label, single-arm, multicenter, Phase 2 study designed to assess objective response via investigator assessment in pediatric patients with relapsed/refractory RMS, NRSTS, and EWS treated with eribulin mesylate. Secondary study objectives included an evaluation of progression-free survival using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, duration of response, and safety and tolerability. There were no confirmed responses among the 21 patients treated with eribulin mesylate.

Eribulin mesylate did not demonstrate clinically meaningful anti-tumor activity in pediatric patients in any of the three completed studies. The safety data in the pediatric patients enrolled in the three studies were consistent with the established safety profile observed in adults treated with eribulin mesylate.

4. Labeling Changes

The Applicant's proposed labeling changes consisted of updates to Section 8.4: Pediatric Use and Section 12.3: Specific Populations. FDA proposed labeling changes are noted with strikethrough deleted text or additions to text in tracked changes format.

All changes proposed by FDA were accepted by the Applicant.

5. Recommended Regulatory Action

No change in the indication for eribulin mesylate is indicated based on the results of pediatric studies. The clinical review team recommends approval of this sNDA.

The Pediatric Exclusivity Determination Request was reviewed by the FDA Pediatric Exclusivity Review Board and it was determined that the Applicant met the terms of the Written Request. Pediatric Exclusivity has been granted to eribulin mesylate (Refer to the Pediatric Determination Checklist granted on August 9, 2022).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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08/31/2022 02:15:47 PM

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