CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201532

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 201532, HALAVEN (eribulin mesylate) Injection
0.5 mg/mL (1 mg/2 mL vial)
Date: 10-NOV-2010

Introduction

HALAVEN (eribulin mesylate) Injection is for the treatment of advanced breast cancer. The approved drug product will be supplied as 1 mg in 2 mL of solution. It is to be diluted in 100 mL normal saline for infusion administration.
ONDQA recommends approval of this NDA.

Administrative

The original submission of this priority 505(b)(1) NDA was received 30-MAR-2010 from Esai, Inc., of Woodcliff Lake, New Jersey. The drug substance is a new molecular entity (NME).

This was a team review. A total of fifteen (15) CMC amendments were reviewed between 02-APR-2010 and 30-SEP-2010.

This NDA is supported by three DMF's and IND 67,193. Consults for PAI (EES acceptable -29-SEP-2010) and Microbiology (09-AUG-2010), and are acceptable.

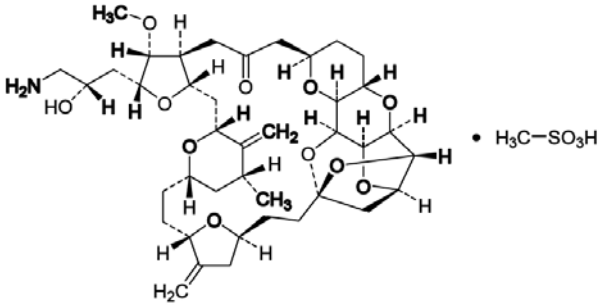
ONDQA recommends approval from the Chemistry, Manufacturing and Controls perspective.

Drug Substance (eribulin mesylate) .

Eribulin mesylate is a complex drug substance with (b) (4) . The manufacturing of eribulin mesylate is a correspondingly (b) (4) During the review, designation of starting materials was a critical deficiency despite the applicant being well informed of this issue by the Agency in meetings as early as April 2006.

However, the applicant did not adequately address these issues prior to filing the NDA. Thus, most of the post-marketing commitments listed herein reflect a balance in having the applicant apply due diligence to establish and control appropriate starting materials while allowing this priority drug product to enter the therapeutic arena in a timely manner so that an important public health need may be addressed.

Chemical structure of eribulin mesylate



Empirical Formula: $C_{40}H_{59}NO_{11} \cdot CH_4O_3S$
Molecular Weight: 826.00 (729.90 for free base)

The approved drug substance retest interval is (b) (4).

Drug Product

Eribulin mesylate injection is formulated as a sterile, clear, colorless solution provided as 1 mg per 2 mL in a (b) (4) vial with (b) (4) The drug product is to be diluted into 100 mL of normal saline (100 mL) and infused.

Unfortunately, the labeled strength is as the mesylate salt. This strength nomenclature contradicts the USP approach that CDER follows. That is; to designate the drug product established name and strength according to the USP salt nomenclature policy (i.e. by neutral species).

The drug product is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Do not freeze or refrigerate A forty eight (48) month expiry is recommended to be approved.

ONDQA recommends approval of this NDA from the CMC perspective.

The following are the post-marketing CMC commitments:

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)

Rik Lostritto, Director, ONDQA Division I

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/s/

RICHARD T LOSTRITTO
11/10/2010

NDA 201532

Eribulin Mesylate Injection

Eisai Pharmaceuticals, Inc.

Ying Wang (Drug Substance)
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment III, Branch VIII

Josephine Jee (Drug Product)
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I, Branch II

For the Division of Drug Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 201532

2. REVIEW #: 1

3. REVIEW DATE: 02-NOV-2010

4. REVIEWER: Ying Wang & Josephine Jee

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (CMC)	30-MAR-2010
Seq. 0001 - Request for Proprietary Name Review	02-APR-2010
Seq. 0004 - Quality Information Amendment – Response to FDA Request	17-MAY-2010
Seq. 0005 - Quality Information Amendment – Revise DP Specifications	07-June-2010
Seq. 0007 - Mtg. Req. -Type C, Starting Materials	22-JUN-2010
Seq. 0009 – Type C Mtg. Starting Materials Mtg.	28-JUN-2010
Seq. 0008 - Response to Potential Review Issues (74 D Letter)	29-JUN-2010
Seq. 0011 - Revised Labels	23-JUL-2010
Seq. 012 - Quality Information Amendment to FDA IR dated 02-JUL-2010	28-JUL-2010
Seq. 0013 - Response to FDA Letter dated 02-JUL-2010	09-AUG-2010
Seq. 0014 - Response to IR dated 29-JUL-2010	09-AUG-2010
Seq. 0016 - Response to IR dated 30-AUG-2010 in response to IR dated 17-SEP-2010	16-SEP-2010
Seq. 0019 - Correspondence Regarding 02-JUL-2010 and 03-SEP-2010 Mtgs.	10-SEP-2010
Seq. 0017- Response to FDA IR Letter dated 30-AUG-2010 and Quality Information dated 16-SEP-2010	24-SEP-2010
Seq. 0020 – Revised Vial and Carton Labels	23-SEP-2010
Seq. 0022 - Draft Labeling	30-SEP-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Eisai Inc.
Address:	300 Tice Boulevard Woodcliff Lake, New Jersey 07677
Representative:	Annmarie Petraglia Senior Director, Global Regulatory Affairs
Telephone:	(201) 949-4516

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: HALAVEN™
b) Non-Proprietary Name (USAN): Eribulin mesylate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antineoplastic (Advanced or Metastatic Breast Cancer)

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 0.5 mg/mL (1 mg/2 mL vial)

13. ROUTE OF ADMINISTRATION: Direct or Intravenous

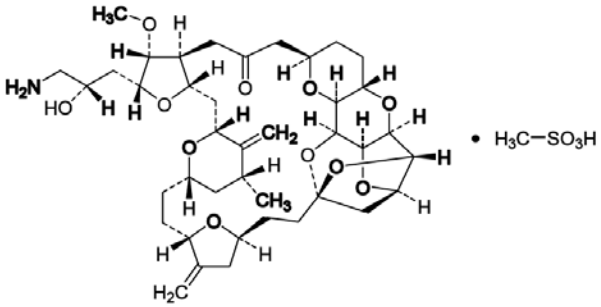
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Structure of Eribulin Mesylate



Empirical Formula: $C_{40}H_{59}NO_{11} \cdot CH_4O_3S$

Molecular Weight: 826.00 (729.90 for free base)

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)				3	Adequate	17-AUG-2009	M. Sassman
				3	Adequate	03-OCT-2007	J. Chang
				3	Adequate	17-APR-2009	M. Stevens-Riley

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 67,193	Eisai Medical Research Inc	E7389	Active	20-APR-2003	None
IND 67,193	Eisai Medical Research Inc	E7389		14-APR-2006	EOP2 meeting minutes

CMC Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug substance and drug product stability data deemed necessary.
EES	Site inspections	29-SEP-2010	Acceptable/ OC	Overall Recommendation - Acceptable
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	20-SEP-2010	L.Koch/ Approval	Recommended to lower the acceptance criteria for impurities (b) (4) in the drug product.
Biopharm	N/A			
ODS/DMEPA	Labeling consult	10-SEP-2010	Loretta Holmes/ Approval	Recommended revisions for Carton and container labels, and PI AMD dated 23-SEP-2010 – Acceptable.
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A		See this review	Applicant cites 21 CFR 25.31(b) as applicable - Acceptable
Microbiology	(b) (4) Manufacturing,	09-AUG-2010	R. Mello/ Approval	Recommended approval.

The CMC Review for NDA 201532

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the chemistry, manufacturing and control (CMC) perspective. The Office of Compliance issued an overall ACCEPTABLE recommendation for all sites listed in this application on September 29, 2010.

Eribulin Mesylate Injection is stored at 25 °C (77 °F); excursions permitted to 15° – 30° C (59° -86° F). Do not freeze or refrigerate. A 48 month expiry date is proposed and granted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following is the post-marketing CMC commitments:

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)

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance, eribulin mesylate, is a (b) (4) It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondira okadai*. Eribulin mesylate is a white powder which is freely soluble in water, methanol, ethanol, 1-octanol, benzyl alcohol, dichloromethane, dimethylsulfoxide, N-methylpyrrolidone and ethyl acetate. It is soluble in acetone, sparingly soluble in acetonitrile, and practically insoluble in tert-butyl methyl ether, n-heptane and n-pentane. Eribulin mesylate is characterized by ion chromatography for counter ion content, and spectroscopic analyses (mass, ultraviolet, nuclear magnetic resonance, single crystal X-ray crystallography, and circular dichroism) for molecular structure and absolute configuration. Bulk drug substance is hygroscopic and sensitive to light, heat, and acid hydrolysis.

The manufacturing of eribulin mesylate is a (b) (4)

(b) (4)

(2) Drug Product

Eribulin Mesylate Injection is formulated as a sterile, clear, colorless aqueous solution intended for dilution into an infusion solution ((b) (4) 0.9% sodium chloride) prior to patient administration or it can be used undiluted. Eribulin Mesylate Injection is diluted in 100 mL of 0.9% of normal saline in the diluted form. Eribulin Mesylate Injection is not recommended to dilute in 5% Dextrose solution. The proposed Eribulin Mesylate Injection contains 1 mg of eribulin mesylate in 2 mL (ethanol:water (5:95)) vial. The proposed presentation consists of Type I (b) (4)

Undiluted (b) (4) erybulin mesylate solution can be stored in the syringe for up 4 hours at room temperature and up to 24 hours under refrigeration.

The proposed drug is manufactured by (b) (4)

(b) (4) These levels also were recommended by Pharmacology/Toxicology based on the safety data.

Eribulin Mesylate Injection is stored at 25 °C (77 °F); excursions permitted to 15° – 30° C (59° -86° F). Do not freeze or refrigerate. A 48 month expiry date is proposed based on 36 months of long term and 6 months accelerated stability data from three primary stability batches, and 48 months of long term and 6 months accelerated stability data from a supportive stability batch.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be used on Days 1 and 8 of a 21-day cycle with dosing as an intravenous infusion in normal saline administered over 2 to 5 minutes at a dose of 1.4 mg/m^2. The proposed indication is for the treatment of patients with locally advanced or metastatic breast cancer who has previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane.

C. Basis for Approvability or Not-Approval Recommendation

A major CMC issue for this NDA is the proper designation of the starting materials for the drug substance. Due to the (b) (4) quality control needs to be (b) (4) The original proposed starting materials by the applicant were (b) (4) All manufacturing process steps (b) (4) starting materials would not be manufactured under cGMP and not subject to regulatory control. This issue was resolved during this review cycle through negotiation with the applicant. The revised designated starting materials are (b) (4) under cGMP control. Additional in-process controls, (b) (4)

This application as amended has provided acceptable drug substance and drug product information, acceptable specifications for the drug substance and the drug product, acceptable analytical method validation. In addition, the Office of Compliance has issued an overall acceptable recommendation for all manufacturing and testing facilities. Microbiology has issued an acceptable recommendation in the (b) (4) sterilization process for the drug product manufacturing. The revised labeling for the vial, carton, and

package insert is also acceptable as evaluated by CMC and DMEPA. Therefore, this NDA is recommended for approval from CMC perspective.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Ying Wang, PhD

Josephine Jee

B. Endorsement Block:

(See appended electronic signature page)

Sarah Pope Miksinski, PhD, Branch Chief/ONDQA

C. CC Block: entered electronically in DFS

W. Adams/acting BC/ONDQA
S. Goldie/PMQ/ONDQA
L. Zhou/CMC Lead/ONDQA
V. Jarral/Regulatory PM/DBOP

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/s/

YING WANG
11/02/2010

JOSEPHINE M JEE
11/02/2010

WILLIAM M ADAMS
11/03/2010
William Adams acting for Sarah Pope Miksinski

Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment

OND Division:	**Division of Biologic Oncology Products**
NDA:	201,532 (e-submission)
Applicant:	Eisai, Inc.
Stamp Date:	30 March, 2010
PDUFA Goal Date:	30 September, 2010 (Priority)
Established Name:	Eribulin Mesylate
Trade Name	Halaven Injection
Dosage Form and Strength:	Injection; 1 mg/2 mL
Route of Administration:	IV
Indication:	for the treatment of patients with (b) (4) MBC previous treated with at least two chemotherapeutic regimens.
eCTD Reference for CMC:	NDA 20-1532 (Module 2 and 3)
Regulatory Filing:	For 505 (b) (1)
Related INDs:	IND 67,193 and IND 64,395
Assessed by:	Liang Zhou

	Yes	No
ONDQA Fileability:	x	

Comments for 74-Day Letter:

Pending reviewer evaluation

Background Summary

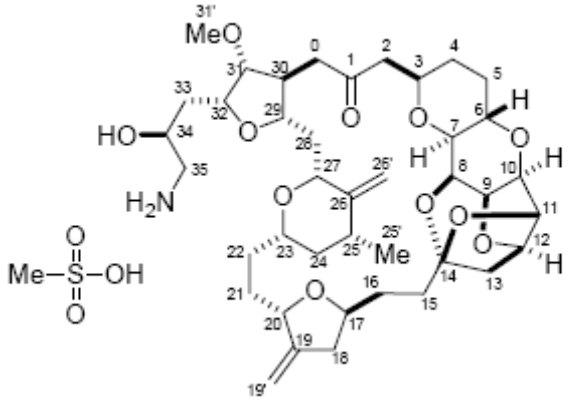
Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin is a structurally simplified synthetic analog of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin inhibits the growth phase of microtubule dynamics without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. This pattern is distinct from that of members of tubulin-targeting classes currently in clinical use, including taxanes, vinca alkaloids, and epothilones. Eribulin retains activity against drug-resistant cells that harbor β-tubulin mutations associated with taxane resistance. Clinical pharmacology studies showed that eribulin has a rapid distribution phase and a prolonged (mean 40 hour) terminal elimination half-life after intravenous (IV) administration. At the proposed human dose, eribulin is not expected to inhibit the metabolism of other drugs administered concurrently. The proposed indication is for the treatment of patients with (b) (4) metastatic breast cancer previously treated with at least two chemotherapeutic regimens when eribulin is administered at a dose of 1.4 mg/m^2 IV over 2-5 minutes on days 1 and 8 of a 21-day cycle.

IND 67,193 was submitted in 2003. The CMC EOP2 and pre-NDA meetings were held on April 14, 2006 and November 23, 2009, respectively. At the CMC EOP2 meeting, it was concluded that the starting material and other related issues were warranted to have further discussion through meetings, teleconference, etc (The Agency stated that (b) (4) may be considered as a starting material for (b) (4); the proposed (b) (4) may be considered as starting materias). starting materials for (b) (4).. However, several IND chemistry amendments were submitted after the CMC EOP 2 meeting and found to be NAI (no action indicated).

Drug Substance (DS)

Eribulin mesylate is a (b) (4).
CAS Name: 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*furo[3,2-*i*]furo [2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl] hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*, 12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt).

Molecular Structure:



Eribulin mesylate is a hygroscopic white powder. It is freely soluble in water, methanol, ethanol, 1-octanol, benzyl alcohol, etc. In the aqueous solution, it is freely soluble at pH 3–7, soluble at pH 9 and slightly soluble at pH 11. Detailed DS information is provided in the submission. Manufacture, packaging, release testing and stability testing are performed at Kashima Plant, Eisai Co., Ltd. (Ibaraki-ken, Japan) (b) (4)

Part of the structure elucidation proof is a characterization of (b) (4) (addressed below).

Proposed Starting Material (b) (4)

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compressed review clock. A team review approach should be considered.

Liang Zhou Pharmaceutical Assessment Lead (PAL)	April 30, 2010 Date
Sarah Pope Miksinski, Ph.D. Branch Chief	May 3, 2010 Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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/s/

LIANG ZHOU
05/03/2010

WILLIAM M ADAMS
05/03/2010
William Adams, acting for Sarah Pope Miksinski