

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201532

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: November 8, 2010

Application Type/Number: NDA 201532

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Subject: Proprietary Name Review

Drug Name: Halaven (Eribulin Mesylate) Injection
1 mg/2 mL (0.5 mg/mL)

Applicant: Eisai Inc.

OSE RCM #: 2010-752

1 INTRODUCTION

This re-assessment of the proprietary name responds to the anticipated approval of NDA 201532 within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Halaven, acceptable in OSE Review 2010-752, dated July 2, 2010 and OSE Review 2007-1003/2007-1004, dated February 1, 2008. Additionally, the Division of Drug Marketing, Advertising and Communications (DDMAC) found the name acceptable from a promotional perspective on May 10, 2007 and April 15, 2010.

2 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 6) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We use the same search criteria outlined in OSE Review 2010-752, for the proposed proprietary name, Halaven. None of the product characteristics for Halaven have been altered since our previous review, thus we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN update. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

3 RESULTS

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of November 5, 2010.

However, the safety evaluator searches of the databases listed in Section 5 identified one additional name, Altavera, thought to look similar to Halaven and represent a potential source of drug name confusion.

Failure mode and effect analysis (FMEA) was applied to determine if the proposed name could potentially be confused with any of the name and lead to medication errors. This analysis determined that the name similarity between Altavera and Halaven was unlikely to result in medication errors for the reasons presented in Appendix A.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Halaven, is not vulnerable to name confusion that could lead to medication errors nor is it considered promotional. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Halaven, for this product at this time.

DMEPA considers this a final review, however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Biologic Oncology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

1. Holmes, L. OSE Review 2010-752: Proprietary Name Review for Halaven. July 2, 2010.
2. Holmes, L. OSE Review 2007-1003/2007-1004: Proprietary Name Review for (b) (4) and Halaven. February 1, 2008.

3. **Drugs@FDA** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

4. **Division of Medication Error Prevention and Analysis proprietary name requests**

This is a list of the proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

5. **USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

APPENDIX

Appendix A: Product with multiple differentiating product characteristics

Proprietary Name Halaven (Eribulin Mesylate) Injection <i>Strength:</i> 1 mg/2 mL (0.5 mg/mL) <i>Dosage:</i> 1.4 mg/m² intravenously on days 1 and 8 of a 21-day cycle	Similarity to Halaven	Reason for Discard
Altavera (Ethinyl Estradiol and Levonorgestrel) Tablets <i>Strength:</i> 0.03 mg/0.15 mg <i>Dosage:</i> One tablet orally once daily	Look	Medication errors unlikely to occur in the usual practice setting due to product characteristic and orthographic differences between the names. Rationale: The products differ in dose (1.4 mg/m ² vs. 1 tablet), route of administration (oral vs. intravenous), frequency of administration (days 1 and 8 of a 21-day cycle vs. once daily), dosage form (injection vs. tablet), and indication of use (prevention of pregnancy vs. treatment of breast cancer). Halaven contains one upstroke letter whereas Altavera contains two. The upstroke letter “t” in Altavera also has a cross-stroke.

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/s/

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**Department of Health and Human Services
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Date: July 2, 2010

To: Patricia Keegan, MD, Director
Division of Biologic Oncology Products

Through: Kristina A. Toliver, PharmD, Team Leader
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Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
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Subject: Proprietary Name Review

Drug Name: Halaven (Eribulin Mesylate) Injection
1 mg/2 mL (0.5 mg/mL)

Application Type/Number: NDA 201532

Applicant: Eisai Inc.

OSE RCM #: 2010-752

*****This document contains proprietary and confidential information that should not be released to the public.*****

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EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of the proposed proprietary name, Halaven, for Eribulin Mesylate Injection, 1 mg/2 mL (0.5 mg/mL). Our evaluation of the proposed proprietary name, Halaven, did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Halaven, conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to an April 2, 2010 request from Esai, Inc. for an assessment of the proposed proprietary name, Halaven, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, the container labels, carton and insert labeling are being evaluated for their potential contribution to medication errors under separate cover (OSE Review 2010-754).

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Halaven, acceptable in OSE Review #2007-1003/2007-1004, dated February 1, 2008 when the product was an investigational new drug (IND #067193). The Division of Drug Oncology Products did not have any concerns with the proposed name, Halaven, and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on May 10, 2007.

1.3 PRODUCT INFORMATION

Halaven is the proposed proprietary name for Eribulin Mesylate Injection. Halaven is a microtubular dynamics inhibitor belonging to the halicondrin class of antineoplastic agents. It is indicated 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. The recommended dosage is 1.4 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Halaven will be supplied in single-use vials and individually packaged in a carton. The vials should be stored in their original cartons at temperatures up to 25°C (77°F).

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Halaven.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter “H” when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{1,2}

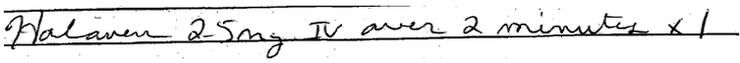
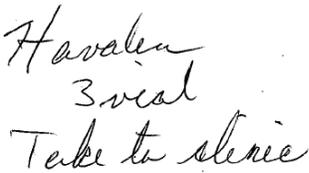
To identify drug names that may look similar to Halaven, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (one, lower case letter “l”), downstrokes (none), cross strokes (none), and dotted letters (none). Additionally, several letters in Halaven may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Halaven.

When searching to identify potential names that may sound similar to Halaven, the DMEPA staff search for names with similar number of syllables (three), stresses (HAL-a-ven, hal-A-ven or hal-a-VEN), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (see Appendix B). The Applicant did not provide their intended pronunciation of the proprietary name in the proposed name submission and, therefore, it could not be taken into consideration. The Applicant’s intended pronunciation of the name is “hal-uh-ven”. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies.

Figure 1. Halaven Prescription Study (conducted on April 22, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u></p> 	<p>Halaven Dispense 3 vials to take to clinic</p>
<p><u>Outpatient Prescription:</u></p> 	

¹ Institute for Safe Medication Practices. Confused Drug Name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

² Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA searches yielded a total of 32 names as having some similarity to the name Halaven.

Twenty-two of the 32 names were thought to look like Halaven. These include Fludara, Nebcin, Astelin, Avelox, Acticin, Balziva, Butisol, Halazone, Flotrin, Hexalen, Nallpen, (b) (4) Flulaval, Artane, Letairis, Lotensen, Flolan, Kadian, Naloxone, Halazepam, Relafen, and Alavert. Three of the names were thought to sound like Halaven. These include Calan, Salagen, and Alophen. The remaining seven names, Aralen, Halfan, Talacen, Halothane, (b) (4), (b) (4), and Halcion were thought to look and sound similar to Halaven.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of April 26, 2010.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Halaven.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 34 practitioners responded. DMEPA notes that the name Halaven was misspelled as “Havalen” on the outpatient prescription sent to practitioners participating in the outpatient written prescription study. None of the 15 responses to the outpatient study were evaluated due to the misspelling. None of the 19 responses that were evaluated overlapped with any existing or proposed drug names. Eleven of the practitioners interpreted the name correctly as “Halaven”. The remainder of the practitioners in the inpatient written study and verbal study misinterpreted the drug name. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS (DBOP)

3.4.1 Initial Phase of Review

In response to the OSE April 29, 2010 e-mail, the Division of Biologic Oncology Products (DBOP) stated “the review team in DBOP has no preliminary comments”.

3.4.2 Midpoint of Review

On May 14, 2010, DMEPA notified DBOP via e-mail that we had no objections to the proposed proprietary name, Halaven. Per e-mail correspondence from the Division of Biologic Oncology Products on May 25, 2010, the Division stated they have “no comments or concerns with DMEPA's draft review of the proposed proprietary name, Halaven”.

3.5 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator did not result in identification of any additional names which were thought to look or sound similar to Halaven and represent a potential source of drug name confusion.

The database searches identified the name “Lotensen.” However we determined that Lotensin was inadvertently misspelled as “Lotensen”. Thus we evaluated Lotensin rather than Lotensen.

4 DISCUSSION

Halaven is the proposed proprietary name for Eribulin Mesylate Injection, 1 mg/2 mL (0.5 mg/mL). This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 PROMOTIONAL REVIEW

DDMAC did not find the name Halaven promotional. The Division of Drug Oncology products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY REVIEW

The review team (e.g., clinical, chemistry, etc.) did not express any concerns with the proposed name. In total, 32 names were identified as potential sources of sound and look-alike confusion. DMEPA did not identify other aspects of the name that could function as a source of error. Twenty-three of the 32 names were not evaluated further for the following reasons: eight names were evaluated in our previous review of this proposed name and the products characteristics have not changed, fourteen names lacked orthographic or phonetic similarity and one name is a proposed name within the Agency (see Appendices D through F).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining nine names and lead to medication errors. This analysis determined that the name similarity between Halaven and the remaining names was unlikely to result in medication errors for the reasons presented in Appendices G and H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Halaven, is not promotional nor is it vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Halaven, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Halaven, and have concluded that it is acceptable. The proposed name, Halaven, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

6 REFERENCES

1. *Micromedex Integrated Index* (<http://csi.micromedex.com>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

3. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. *FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]*

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

7. *Electronic online version of the FDA Orange Book* (<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. *U.S. Patent and Trademark Office* (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

9. *Clinical Pharmacology Online* (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. *Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at* (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. *Natural Medicines Comprehensive Databases* (www.naturaldatabase.com)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. *Stat!Ref* (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. *USAN Stems* (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. *Red Book Pharmacy's Fundamental Reference*

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. *Lexi-Comp* (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

17. *Medical Abbreviations Book*

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁵ DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	<i>Potential causes of drug name similarity</i>	<i>Attributes examined to identify similar drug names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the

proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and

identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely effect of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

⁶ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in proposed name “Halaven”	When scripted may appear as:	When spoken may be interpreted as:
Capital “H”	A, Fl, or T	Ah
lower case “a”	ce, ci, d, e, o, u	e, o, u
lower case “l”	e, undotted “i”, uncrossed “t”	
lower case “v”	c, L, m, r, u	vin, phen
lower case “e”	a, c, undotted “i”, l, o	a or i
lower case “n”	b, h, m, r, v	in,

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Halaven	Havalea	Halaven
Halaven	Havalen	Halavent
Halaven	Havalen	Halavin
Halaven	Havalen	Halivent
Halaven	Havalen	Haloven
Halaven	Havalen	Haloven
Halaven	Havalen	Haloven
Halaven	Havalen	Halovend
Halaven	Havalen	
Halaven	Havalen	
Halavenn	Havalen	
	Havalen	
	Havalen,	
	Havalen,	
	Havalen,	

The outpatient sample was misspelled.

Appendix D: Names evaluated in our previous proprietary name review. Neither the product characteristics of Halaven or these products have changed since our previous review (OSE Review #2007-1003/2007-1004)

Name	Name
Halazone	Salagen
Nallpen	Halfan
Nalfon	Talacen
Alavert	Halcion

Appendix E: Names Lacking Orthographic and/or Phonetic Similarity.

Name	Similarity to Halaven
Astelin	Look
Avelox	Look
Aticin	Look
Balziva	Look
Butosol	Look
Flotrin	Look
Letairis	Look
Flolan	Look
Kadian	Look
Halazepam	Look
Calan	Sound
Aralen	Look and Sound
Halothane	Look and Sound

Appendix F: Proposed names within the Agency

Proposed Proprietary Name	Similarity to Halaven	Comments
(b) (4)		

Appendix G: Names of products with numerical overlap or similarity in strength, dose or achievable dose with multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Halaven	Strength	Signa	Differentiating Product Characteristics (Halaven vs. Product)
Halaven	N/A	1 mg/2 mL (0.5 mg/mL)	1.4 mg/m ² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle	N/A
Alophen (Bisacodyl) OTC Product	Sound	Tablets: 5 mg	5 mg to 15 mg orally once daily	<p><i>Route of administration:</i> Intravenous vs. oral</p> <p><i>Dosage form:</i> Injection vs. tablet</p> <p><i>Frequency of administration:</i> Day one and day eight of a 21-day cycle vs. once daily</p> <p><i>Dose specification on a prescription:</i> The Halaven dose (i.e., 1.4 mg/m²) as well as the calculated dose would likely be specified vs. Alophen prescriptions would say ‘1 tablet’ or X mg. Additionally, the only strength of Alophen is 5 mg, whereas doses of Halaven will unlikely be higher than 3 mg (based on a BSA of 2). The dose in conjunction with the differences in route of administration when pronounced will help differentiate these products.</p>

*** This document contains proprietary and confidential information that should not be released to the public.***

Product name with potential for confusion	Similarity to Halaven	Strength	Signa	Differentiating Product Characteristics (Halaven vs. Product)
Halaven	N/A	1 mg/2 mL (0.5 mg/mL)	1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle	N/A
Lotensin (Benazepril Hydrochloride) Tablets	Look	5 mg, 10 mg, 20 mg, and 40 mg	5 mg to 80 mg orally once daily or in divided doses	<p><i>Route of administration:</i> Intravenous vs. oral</p> <p><i>Dosage form:</i> Injection vs. tablet</p> <p><i>Frequency of administration:</i> Day one and day eight of a 21-day cycle vs. once daily</p> <p><i>Dose specification on a prescription:</i> The Halaven dose (i.e., 1.4 mg/m²) as well as the calculated dose would likely be specified. Additionally the lowest strength of Lotensin is 5 mg, whereas doses of Halaven will unlikely be higher than 3 mg (based on a BSA of 2).</p>
Flulaval (Influenza Virus Type A and B Vaccine)	Look	Not applicable	0.5 mL intramuscularly once	<p>Flulaval contains the upstroke letter “l” in 3 positions whereas Halaven only contains one letter “l” which may help to differentiate the names.</p> <p><i>Route of administration:</i> Intravenous vs. intramuscular</p> <p><i>Dose specification on a prescription:</i> The Halaven dose (i.e., 1.4 mg/m²) as well as the calculated dose would likely be specified on a prescription vs. 0.5 mL. Although the milliliter amount could overlap, since Halaven is a chemotherapeutic drug it is unlikely that it will be prescribed in milliliters.</p>

Product name with potential for confusion	Similarity to Halaven	Strength	Signa	Differentiating Product Characteristics (Halaven vs. Product)
Halaven	N/A	1 mg/2 mL (0.5 mg/mL)	1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle	N/A
<p>Relafen (Nabumentone) Tablets</p> <p>This product has been discontinued, however, generics are available</p>	Look	500 mg and 750 mg	<p>1 g to 2 g per day. Give once daily or in divided doses (e.g., 1 g orally once daily or 500 mg orally twice daily</p>	<p>The upstroke and downstroke of the letter “f” in Relafen may help to differentiate the names.</p> <p>The beginning letters R vs. H and their corresponding sounds in conjunction with pronunciation of the route of administration will help differentiate the names phonetically.</p> <p><i>Route of administration:</i> Intravenous vs. oral</p> <p><i>Dosage form:</i> Injection vs. tablets</p> <p><i>Frequency of administration:</i> Day one and day eight of a 21-day cycle vs. once daily or twice daily</p> <p><i>Dose specification on a prescription:</i> The Halaven dose (i.e., 1.4 mg/m²) as well as the calculated dose would likely be specified on a prescription. Additionally, the maximum dose of Halaven will likely be less than 3 mg (based on a BSA of 2). Thus the dosing differences of 3 mg and 500 mg/750 mg will help differentiate the names.</p>

Appendix H: Names of products with numerical similarity in strength or dose

Proprietary Name: Halaven	Strength: 1 mg/2 mL (0.5 mg/mL)	Signa: 1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p>Nebcin (Tobramycin Sulfate) Injection</p> <p><i>Strength:</i> 20 mg/2 mL (10 mg/mL) 60 mg/1.6 mL (40 mg/mL) 80 mg/2 mL (40 mg/mL)</p> <p><i>Dosage:</i> 1.5 mg to 5 mg per kg per day intravenously or intramuscularly in equally divided doses every 8 hours; every 12 hours; every 24 hours; every 48 hours; or every 72 hours</p> <p>This product has been discontinued, however, generics are available</p>	<p>Orthographic similarity: The beginning letters “H” and “N” may look similar when scripted in lower case. The letters that follow (“al” vs. “eb”) may look similar. Both names end with the letter “n”.</p> <p>The vial volumes overlap (i.e., 2 mL). Additionally, the number “2” overlaps between a 2 mg dose of Halaven and the 20 mg strength of Nebcin.</p>	<p>Medication errors are unlikely to occur due to product characteristic and orthographic differences between the names.</p> <p><i>Rationale:</i></p> <p>Halaven contains seven letters and appears longer in length when compared to Nebcin which contains six letters.</p> <p>Although the vial volumes overlap, it is unlikely the dosage for either product will be prescribed based on the volume of drug to be administered. Instead, a prescription will most likely state the number of milligrams to be administered.</p> <p>Additionally, since Halaven is a chemotherapeutic agent and it is dosed based on body surface area (BSA), it is likely the patient’s BSA will be stated on an order along with the calculated dose. Furthermore, chemotherapy orders are typically written on a special order sheet or with a heading that indicates that the prescription(s) that follows is for a chemotherapeutic agent or regimen.</p>
<p>Hexalen (Altretamine) Capsules</p> <p><i>Strength:</i> 50 mg</p> <p><i>Dosage:</i> 260 mg/m² per day (round dose to the nearest 50 mg). The usual dose is 400 mg orally per day. Give in 3 to 4 divided doses (e.g., 100 mg orally four times per day)</p>	<p>Orthographic similarity: Both names contain seven letters and share identical letters in the first, third, sixth, and seventh positions (i.e., H-a-e-n).</p> <p>Both products are chemotherapeutic agents.</p>	<p>Medication errors are unlikely to occur due to orthographic and product characteristic differences.</p> <p><i>Rationale:</i></p> <p>The upstroke letter “l” is in the third position in Halaven and in the fifth position in Hexalen which helps to differentiate the names. Additionally, Hexalen contains the cross-stroke letter “x” which further helps to differentiate the names.</p> <p>Halaven and Hexalen differ in route of administration (intravenous vs. oral) and frequency of administration (once, on days 1 and 8 of a 21-day cycle vs. three or four times per day).</p>

Proprietary Name: Halaven	Strength: 1 mg/2 mL (0.5 mg/mL)	Signa: 1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p>Fludara (Fludarabine Phosphate) for Injection</p> <p>Strength: 50 mg</p> <p>Dosage: 25 mg/m² intravenously on five consecutive days, every 28 days</p>	<p>Orthographic similarity: When scripted in close proximity, the letters “Fl” may look like the letter “H”. The letters “ave” in Halaven may look similar to the letters “ara” in Fludara.</p> <p>Both products are chemotherapeutic agents administered by the intravenous route.</p> <p>The number “5” overlaps between the 0.5 mg/mL concentration of Halaven and the 50 mg strength of Fludara.</p>	<p>Medication errors are unlikely to occur due to orthographic and product characteristic differences between the names.</p> <p><i>Rationale:</i></p> <p>The ending letter “n” in Halaven may help to differentiate the name pair because it makes the name appear longer in length as compared to Fludara.</p> <p>Halaven and Fludara have a different frequency of administration (once, on days 1 and 8 of a 21-day cycle vs. once daily for 5 consecutive days).</p> <p>Although the number “5” overlaps between the 0.5 mg/mL concentration of Halaven and the 50 mg strength of Fludara it is unlikely that the Halaven concentration (0.5 mg/mL) would be specified on an order since it is not necessary to have it there in order for the prescription to get filled correctly.</p> <p>Additionally, the dose would be specified on orders for Halaven and Fludara. This would help to differentiate the names since the doses do not overlap and doses of Halaven would unlikely exceed 3 mg.</p>

Proprietary Name: Halaven	Strength: 1 mg/2 mL (0.5 mg/mL)	Signa: 1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p>Naloxone Injection</p> <p><i>Strength:</i> 0.4 mg/mL, 0.8 mg/2 mL, 4 mg/10 mL</p> <p><i>Dosage:</i> 0.1 mg to 2 mg intravenously, intramuscularly, or subcutaneously every 2 to 3 minutes</p>	<p>Orthographic similarity: The beginning letters of the names may look similar “Hala” vs. “Nalo”. Additionally, the letters “en” in Halaven may look similar to the letters “on” in Naloxone.</p>	<p>Medication errors are unlikely to occur due to orthographic and product characteristic differences.</p> <p><i>Rationale:</i></p> <p>The cross stroke letter “x” in Naloxone may help to differentiate the names.</p> <p>Although the products share an overlapping dose (2 mg), Halaven is a chemotherapeutic agent and it is dosed based on body surface area (BSA). Therefore, it is likely the patient’s BSA will be stated on an order along with the calculated dose. Furthermore, chemotherapy orders are typically written on a special order sheet or with a heading that indicates that the prescription(s) that follows is for a chemotherapeutic agent or regimen. This would not be the case with Naloxone</p>

Proprietary Name: Halaven	Strength: 1 mg/2 mL (0.5 mg/mL)	Signa: 1.4 mg/m² intravenously over two to five minutes on days 1 and 8 of a 21-day cycle
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p>Artane (Trihexyphenidyl Hydrochloride) Tablets Elixir</p> <p><i>Strength:</i> Tablets: 2 mg and 5 mg Elixir: 2 mg/5 mL</p> <p><i>Dosage:</i> Dosage should be individualized. Dosage range is 1 mg to 15 mg daily.</p>	<p>Orthographic similarity: The beginning letters (“H” vs. “A”) may look similar when scripted. The upstroke letters “l” vs. “t” may look similar if the letter “t” is not crossed. Additionally, the ending letters “aven” vs. “ane” may look similar if the letter “n” in Halaven is trailed off when scripted.</p> <p>Both products may share an overlapping doses (e.g., 2 mg and 3 mg)</p>	<p>Medication errors unlikely to occur due to product characteristic differences.</p> <p><i>Rationale:</i></p> <p>Although the products may share overlapping doses (e.g., 2 mg and 3 mg), Halaven is a chemotherapeutic agent and it is dosed based on body surface area (BSA). Therefore, it is likely the patient’s BSA will be stated on an order along with the calculated dose. Furthermore, chemotherapy orders are typically written on a special order sheet or with a heading that indicates that the prescription(s) that follows is for a chemotherapeutic agent or regimen. This would not be the case with Naloxone.</p> <p>Additionally, the route of administration would likely be specified on an order for Halaven since it is a chemotherapeutic agent and careful attention is usually taken to ensure such information is specified when prescribing these agents.</p> <p>Artane has been discontinued and the last recorded sales were in 2003⁷. However, Trihexyphenidyl Hydrochloride is available generically from multiple companies.</p>

⁷Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at (www.thomson-thomson.com). Accessed on June 14, 2010.

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

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/s/

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