CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

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Division of Medication Errors and Technical Support HFD-420

PRODUCT NAME: **Ixempra** (Ixabepilone) for Injection 15 mg/vial, 45 mg/vial **NDA #:** 22-065	**NDA SPONSOR:** Bristol-Myers Squibb Company

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Ixempra. This is considered a final decision. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. Please copy DMETS on any correspondence to the sponsor pertaining to this review.

2. DMETS recommends the implementation of the labeling revisions outlined in Section II and III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Ixempra, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Sam Chan, OSE Project Manager, at 301-796-2283.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO 22; Mail Stop 4447
Center for Drug Evaluation and Research

Proprietary Name, Label, and Labeling Review

DATE OF REVIEW: July 13, 2007

NDA #: 22-065

NAME OF DRUG: Ixempra
(Ixabepilone for Injection)
15 mg/vial, 45 mg/vial

NDA HOLDER: Bristol-Myers Squibb Company

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150), for re-review and assessment of the proprietary name, Ixempra, regarding potential confusion with other proprietary or established drug names. This name was previously reviewed and found acceptable in OSE review# 05-0092 dated March 25, 2005. Container labels, carton and insert labeling were submitted on April 16, 2007 and September 14, 2007 for review and comment from a medication errors perspective.

PRODUCT INFORMATION

Ixempra is indicated for the treatment of metastatic or locally advanced breast cancer as monotherapy and in combination with capecitabine. The recommended dose is 40 mg/m^2 administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2m^2 should be calculated based on 2.2m^2. Ixempra is supplied in two strengths, 45 mg and 15 mg. It is provided as a combination package containing one vial of 15 mg Ixempra and one vial of 8 mL Vehicle for Constitution; or one vial of 45 mg Ixempra and one vial of 23.5 mL Vehicle for Constitution. Ixempra must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F). Additionally it is recommended to keep in the original package to protect from light.

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II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Ixempra to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, drug product characteristics of a product must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Ixempra. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the proposed proprietary name, Ixempra, from a promotional perspective.

2. The Expert Panel identified five (5) names that were thought to have potential for confusion with Ixempra. This includes: Prempro, Suprane, Oxandrin, Ixemprah, and Ixemprya.

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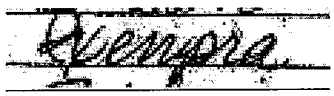
[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Ixempra 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. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Ixempra. These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were 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 sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Requisition #1: 	"Ixempra – order code 4430 – 3 vials"
Requisition #2: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to a currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

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C. SAFETY EVALUATOR RISK ASSESSMENT

When evaluating Ixempra, we reviewed the potential for name confusion and evaluated the products' label and labeling using failure modes and effects analysis (FMEA) and employing principals of human factors. During this analysis we did not identify issues with the proposed name but found many opportunities for error due to the product label and package design. The assessments of the name, container label, carton and insert labeling follow.

1. Look-Alike, Sound-Alike Name Assessment

In reviewing the proprietary name Ixempra, the following five (5) names were identified as having a similar sound or appearance to Ixempra: Prempro, Suprane, Oxandrin, Ixemprah, and Ixemprya.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Ixempra.

Upon initial review, DMETS determined that four names, Suprane, Oxandrin, Ixemprah and Ixemprya would not pose significant risk for confusion for the following reasons: Suprane and Oxandrin are either no longer marketed, are not marketed in the US, are not indicated for human use, or have differentiating product characteristics compared to Ixempra, such as product strength, indication for use, frequency of administration, route of administration, and/or dosage formulation. Additionally, the names lacked convincing look-alike and sound-alike similarities with Ixempra. DMETS also notes that Ixemprah and Ixemprya are registered trademarks with the sponsor in several foreign countries (Spain, France, Austria, Canada, Mexico, United Kingdom and Japan) Additionally, there was limited information available regarding these products. The fact that these products are available in foreign markets and information is unavailable in commonly used U.S. references should minimize the potential for confusion.

The remaining name, Prempro is listed in Table 1 (page 6). Upon further review of potential confusion between Ixempra and Prempro, we determined this name pair would have minmal risk for confusion. This evaluation is discussed in detail following Table 1.

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Table 1: Potential Look-Alike and Sound-Alike Names Identified by DMETS Expert Panel.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Ixempra	Ixabepilone injection	Treatment of patients with metastatic or locally advanced breast cancer after failure of cytotoxic chemotherapy: 40 mg/m^2 administered intravenously over 3 hours every 3 weeks	NA
Prempro	Conjugated estrogens and Medroxyprogesterone Acetate (MPA) tablet 0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, and 0.625 mg/5 mg	Treatment of moderate to severe vasomotor symptoms associated with menopause (intact uterus); treatment of atrophic vaginitis; osteoporosis (prophylaxis): One conjugated estrogen 0.3 mg/MPA 1.5 mg tablet daily titrated to 0.625 mg/MPA 5 mg tablet if necessary (in patients with bleeding or spotting, once malignancy has been ruled out)	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

We examined the orthographic similarities between and Ixempra. Prempro is used to treat moderate to severe vasomotor symptoms associated with menopause, for treatment of atrophic vaginitis, and as prophylaxis for osteoporosis.The look-alike similarities between Ixempra and Prempro stem from the fact both of these names share the letters '-empr-' within the body of their names. Additionally these names both contain seven letters making them similar in length. However, the first two letters look distinct from each other ('Pr-' in Prempro vs. 'Ix-' in Ixempra) when scripted (see below).

Additionally, Ixempra and Prempro do not share product characteristics. Their dosage form (injection vs. tablet), route of administration (intravenous vs. oral) and dosing frequency (every 3 weeks vs. once daily) are all different. Furthermore, Prempro is available in several different combinations strengths whereas Ixempra is individually dosed based upon the patient's body surface area. Hence the prescriber would have to specify a dose for either product. Additionally, an order for Ixempra would indicate the infusion rate as well which should help to further distinguish the names.

Based upon orthographic and product characteristic differences, DMETS feels these two names can coexist in the marketplace with minimal potential for confusion.

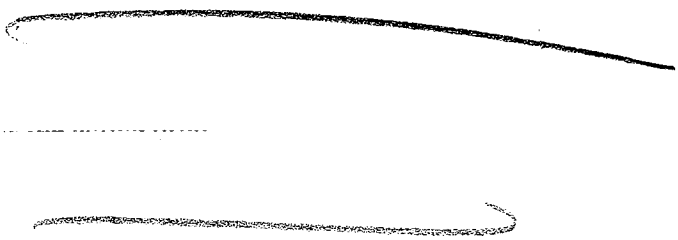
2. Medication Error Analysis of the Label, Labeling and Packaging

Following a systematic review of the draft container label, carton and insert labeling using FMEA and applying the principals of human factors, we have identified numerous ways in which the product design of Ixempra may lead to medication errors when introduced into the U.S. medication use system. Most notably, DMETS believes that the labeling and packaging of this product will perpetuate errors in the prescribing, preparation/dispensing and administration phases of the medication use system. An abbreviated list of the failure modes identified during the prescribing, product preparation, dispensing and administration phases are described below. These represent DMETS' greatest concerns in each area. Given these safety risks, DMETS believes that reformulation of the product to lessen the complex preparation process or at a minimum modifications to the labels, labeling, packaging and healthcare provider education are needed to mitigate these failure modes. Section B provides recommendations based upon these analyses.

Prescribing Phase of the Medication Use System

Failure Mode (What Can Go Wrong?)	**Causality (How Can It Go Wrong?)**
Omission of the "pre-medication" order when ordering Ixempra.	• An H_1 and an H_2 antagonist must be given 1 hour before administration of Ixempra to minimize the chance of a hypersensitivity reaction. This is important information that only appears in the dose and administration section and is not repeated in other sections. Thus, it could be overlooked by the prescriber leading to negative patient outcomes.
Wrong dose ordered	• The dosing instructions are ambiguous. For example, under 'Dosage and Administration, it is stated that the recommended dose is 40 mg/m^2 and doses for patients with body surface areas greater than 2.2 m^2 should be calculated based on 2.2 m^2. These statements could lead a practitioner to believe that 88 mg of drug should not be exceeded (40 mg/m^2 x 2.2 m^2 = 88 mg). • The physician may order the dose using trailing zeros. Terminal zeros are used in the dosage and administration section of the labeling. This may be interpreted by the prescriber as the way to order the product.

Dispensing Phase of the Medication Use System

Failure Modes (What Can Go Wrong?)	Causality (How Can It Go Wrong?)
1. Wrong diluent used to prepare product	• Bottles are not physically linked in carton. • There is a strong likelihood that the vials containing the diluent and active drug will be separated and removed from the outer carton due to space constraints of the pharmacy refrigerator. Therefore, the active drug may be reconstituted with other commonly used diluents (e.g., sodium chloride for injection or sterile water for injection) instead of the provided diluent.
2. Diluent confused for active drug	• 
3. Dose miscalculation	• The actual vial content for the active drug is misleading and confusing to pharmacy personnel compounding the finished product. For example, according to the labeled strength, after adding 8 mL of diluent to the 15 mg vial, the mg/mL concentration would be 1.875 mg/mL (not 2 mg/mL as stated in the labeling). • DMETS notes the use of trailing zeros in the insert labeling. The use of trailing zeros may result in error as decimals may be overlooked leading to an overdose. The practitioner checking the dose may overlook the decimal point and calculate the dose using terminal zeros.
4. Improper or omission of in-line filter step	• Depending on each institution's protocol, the filter can be dispensed at the pharmacy level or attached by a nurse prior to administration. • Under Instructions for Preparation and IV Administration (Section 2.4), it is stated that the infusion must be administered through an appropriate in-line filter with a microporous membrane of 0.2 to 1.2 microns. This information is not repeated in other sections and could be overlooked leading to negative patient outcomes. This is important information as most drugs do not require this kind of special filter prior to administration. • Additionally, because this tubing is not usually utilized, there is the potential for other tubing to be used for administration since this required tubing is not provided.

5. Improper storage	• Pharmacy and nursing personnel may overlook storage requirements because the statement 'refrigerate' lacks prominence. The "refrigerate" statement is in small font and appears in the lower part of the container labels and carton labeling for both the diluent and active drug vial. Proper storage requirements may be overlooked as a result of the lack of prominence.
6. Wrong strength selected and prepared	• The carton labeling for both strengths use the same color scheme. The strength '45 mg/vial' is in but this alone does not offer sufficient prominence or distinction to avoid product selection errors. The size of the strength is small which negates any differentiation by the colors red and blue. • Strengths are stored side by side in the refrigerator.

II. LABELING, PACKAGING AND SAFETY RELATED ISSUES

Following analysis of the container labels, carton and insert labeling DMETS identified several failure modes as a result of the product design and proposed labels and labeling. We therefore recommend the following changes to the labels and labeling to minimize potential medication errors:

1. DMETS recommends the drug vial and diluent be physically linked together in some manner. We recognize the vials are contained in a single carton. However, this may not be adequate to ensure the diluent and vial are not separated due to space constraints in the refrigerator. The use of plastic rings binding both products may lessen the likelihood of storage of the drug and diluent in different places and avert the possibility of not using this diluent or use of an inappropriate diluent.

2. DMETS does not recommend using the same font for the proprietary name, Ixempra on the diluent vial. The name 'Ixempra' should appear smaller than the word 'diluent'. Additionally, a different color scheme on the diluent vial should be used to differentiate this vial from the active drug vial.

3. The container label of the 45 mg/vial should state '47 mg/vial' and the 15 mg/vial should state '16 mg/vial'. Otherwise, the pharmacist will not calculate the correct amount based on the label. If this presentation remains, then at a minimum a statement must be included that indicates the resultant concentration per mL once reconstituted. For example, 'Once reconstituted with XX mL of enclosed diluent, the resultant concentration is 2 mg/mL'. This statement should appear prominently on the principal display panel.

4. Revise the color scheme used to designate the strengths. Use contrasting color, boxing of strengths or other means to distinguish the container label of the 45 mg/vial and the 15 mg/vial from each other.

5. Following the statement 'Doses for patients with body surface area (BSA) greater than $2.2m^2$ should be calculated based on $2.2\ m^2$, please add

6. Increase the prominence of the word, 'refrigerate' to increase the potential for following proper storage instructions.

7. Add a general statement regarding pre-medication and special tubing requirements under section 2.1 in addition to the information in sections 2.3 and 2.4.

8. Delete all trailing zeros throughout the insert labeling.

9. Include the required tubing with an in-line filter with packaging to avoid administration errors.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. If you have further questions, or need clarifications, please contact Sam Chan, OSE project manager, at (301) 796-2283.

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Appendix A:

Ixempra
(Ixabepilone for Injectionl)
NDA# 22-065

Outpatient Written	Inpatient Written	Voice
Ixempra		Izempra
Ixenipra	Ixempra	Izempra
Iemipra	Ixempra	Izempra
Ixenipra	Ixempra	Izepra
	Ixempra	Idempra
Ixempra	Ixempra	Izempra
Ixempra	Ixempra	Isempra
Exenipra	Ixempra	Izempra
Ixempra	Ixempra	Inepra
Xenpra	Ixempra	Eixempra
Exempra	Sxempra	Izempra
Ixenpra	Ixempra	Izempra
	Sxempra	Izempra
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/s/

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