

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-303**

**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**

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Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): Treanda (Bendamustine Hydrochloride) for Injection, 100 mg

Application Type/Number: NDA # 22-303

Applicant: Cephalon Inc.

OSE RCM #: 2008-1681

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## **EXECUTIVE SUMMARY**

The results of the Proprietary Name Risk Assessment found that the name, Treanda with the expanded indication and dose, is not vulnerable to name confusion that could lead to medication errors. Thus, we do not object to the use of the proprietary name Treanda with this expanded dose and indication.

The results of the Label and Labeling Risk Assessment found areas of vulnerability which could lead to medication errors. A detailed discussion can be found in Section 4.2. We acknowledge that the sponsor intends to incorporate the label and labeling recommendations discussed during the October 22, 2008 teleconference.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted on October 22, 2008 by the Office of New Drug Quality Assessment to review the label and labeling revisions for this New Drug Application because the Applicant indicated there had been confusion upon reconstitution of the vials. Additionally, DMEPA was invited to participate in a teleconference with the Applicant and Division which also took place on October 22, 2008. Upon evaluation of the labels and labeling DMEPA noted a new indication of use and dose.

The Applicant submitted this NDA which provides for the expansion of the indication of use to treat indolent B-cell non-Hodgkin's lymphoma (NHL) with a new dosage recommendation of 120 mg/m<sup>2</sup> over 60 minutes. In addition to reviewing the labels and labeling, DMEPA also assessed whether the new indication of use and dose would contribute to potential name confusion between Treanda and currently marketed products. Due to the time constraints provided by the upcoming PDUFA date of October 31, 2008, DMEPA will provide an abbreviated review.

### **1.2 REGULATORY HISTORY**

Treanda was approved March 20, 2008 for the treatment of lymphocytic leukemia. DMEPA found the proposed name Treanda acceptable in OSE Review (2007-2064, dated March 6, 2008). We also provided recommendations for label and labeling revisions to minimize the potential for medication errors.

### **1.3 PRODUCT INFORMATION**

Treanda is currently indicated for the treatment of lymphocytic leukemia with a recommended dose of 100 mg/m<sup>2</sup> over 30 minutes on days 1 and 2 of a 28 day cycle for up to 6 cycles. The new NDA provides for a new indication for indolent B-cell non-Hodgkin's lymphoma with a recommended dose of 120 mg/m<sup>2</sup> over 60 minutes on days 1 and 2 of a 21 day cycle for up to 8 cycles. Treanda must be reconstituted and diluted prior to use. Treanda will continue to be supplied as single-use 20 mL vials containing 100 mg of Bendamustine hydrochloride.

## **2 METHODS AND MATERIALS**

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of

the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division 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.<sup>1</sup>

## **2.1 PROPRIETARY NAME RISK ASSESSMENT**

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proprietary name, Treanda with the expanded indication and new dose, and the proprietary and established names of drug products existing in the marketplace.

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 proprietary name with the expanded indication and new dose. The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>2</sup> FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to Treanda in the previous review could cause confusion that subsequently leads to medication errors in the clinical setting with the new indication and dose. We use the clinical expertise of the Medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the product.

### ***2.1.1 Initial Treanda Proprietary Name Review***

Since this product was approved with a different dose, this review will re-assess the names which were evaluated in the previous review (OSE #2007-2064) using both doses [i.e., approved (100 mg/m<sup>2</sup>) and proposed (120 mg/m<sup>2</sup>)].

### ***2.1.2 Adverse Event Reporting System***

DMEPA conducted a search of the Adverse Event Reporting (AERS) database using the high level terms "maladministration", "medication monitoring errors", and "medication errors due to accidental exposures", preferred terms "accidental overdose", "multiple drug overdose", multiple drug overdose accidental", pharmaceutical product complaint", as well as the active ingredient "Bendamustine" and "Bendamustine Hydrochloride" and the verbatim term "Treanda" on October 22, 2008.

### ***2.1.3 Safety Evaluator Risk Assessment of the Proprietary Name with New Indication and Dose***

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion with the new indication and dose. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>3</sup> When applying FMEA to

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>.

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

assess the risk of a proprietary name, the Division seeks to evaluate the potential for a name to be confused with another drug name as a result of the name confusion and 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 look- or sound-alike 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 Treanda with the new indication and dose, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the product with the new indication is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the 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.

The Safety Evaluator compares the proprietary name to all the names previously reviewed 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 and dose similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated 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 or if post-marketing reports of medication errors involving nomenclature are identified with the currently marketed product and these medication errors will increase if the new dose is approved; then DMEPA will use the FMEA findings to identify strategies to reduce the risk of medication errors or may ultimately request an alternate name. If none of these conditions are met, then we will not object to the use of the proprietary name with the new indication and dose.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant; Furthermore, we contend that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

## **2.2 LABEL AND LABELING RISK ASSESSMENT**

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>4</sup>

Because the Medication Error Prevention staff analyzes reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product, the review division forwarded the following revised label and labeling for our review that were submitted by the Applicant on September 5, 2008 (See Appendix E and F):

- Container Label
- Carton Labeling
- Insert Labeling (no image)

## **3 RESULTS**

### **3.1 PROPRIETARY NAME RISK ASSESSMENT**

#### ***3.1.1 Initial Treanda Proprietary Name Review***

The initial Treanda proprietary name review identified 11 names which sound-alike or look-alike to Treanda to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice setting. The names Trandate, Trionate, Trinate, Tripedia, Triant HC, Namenda, and (b) (4) were thought to look like Treanda. Trientine and Ziana was thought to sound like Treanda. Trental and Truvada were thought to both look and sound like Treanda.

#### ***3.1.2 Adverse Event Reporting System***

The search on October 22, 2008 yielded no cases, however the Applicant submitted seven cases that were received from April 22, 2008 to August 6, 2008. All seven cases involved reconstitution issues.

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<sup>4</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- 3 cases involved reconstitution with sterile water for injection and complained of dissolution issues.
- 2 cases involved an unreported solution used to reconstitute and complained of particulate matter.
- 2 cases involved reconstitution with normal saline and complained of particulate matter.

### ***3.1.3 Safety evaluator risk assessment***

A total of eleven names were analyzed to determine if the drug names could be confused with Treanda with the expanded dose and if the drug name confusion would likely result in a medication error as a result of the expansion in dose.

Failure modes and effects analysis (FMEA) was then applied to determine if the name Treanda with the expanded indication of use and dose could potentially be confused with any of the eleven names and lead to medication error. This analysis determined that the name similarity between Treanda and the identified names was unlikely to result in medication errors for the eleven product names for the reasons identified in (Appendix B through D).

## **3.2 LABEL AND LABELING RISK ASSESSMENT**

We note that the revised labels and labeling include most of our recommendations from our previous review (OSE Review 2007-2064) which will address the reconstitution confusion identified in the post-marketing cases. However, review of the revised container labels have found additional areas of vulnerability that could lead to medication error.

### ***3.2.1 Container Label***

The single-use vial statement is not in conjunction with the discard unused portion statement.

### ***3.2.2 Carton Labeling***

The single-use vial statement is not in conjunction with the discard unused portion statement on the principal display panel.

The side panel of the carton label is cluttered and difficult to read.

### ***3.2.4 Package Insert Labeling***

The difference in infusion times for each indication is not emphasized.

## **4 DISCUSSION**

### **4.1 PROPRIETARY NAME RISK ASSESSMENT**

The results of the Proprietary Name Risk Assessment found that the name, Treanda with the expanded indication of use and dose, is not vulnerable to name confusion that could lead to medication errors.

### **4.2 LABEL AND LABELING RISK ASSESSMENT**

We note the Applicant has addressed most of our label/labeling recommendations from our previous review, however, the Label and Labeling Risk Assessment found additional areas of vulnerability that could lead to medication errors.

#### ***4.2.1 Container Label***

This product is for single use only and therefore it should be clearly communicated that any unused portion should be discarded. Presenting discard information on the container labels and carton labeling will decrease the potential for practitioners to use the vial for multiple doses and convey that any remaining medication should not be saved for subsequent doses. The discard unused portion statement should be in conjunction with the single use vial statement to ensure that any product that is left over from use is discarded.

#### ***4.2.2 Carton Labeling***

The carton labeling should also contain the discard unused portion statement in conjunction with the single use vial statement to ensure that any product that is left over from use is discarded. This should be located on the principle display panel.

The side panel of the carton is cluttered and difficult to read. Additionally, the reconstitution and dilution instructions are too close to one another. This presentation increases the risk that practitioners will confuse the solution required for reconstitution (sterile water for injection) with the solution required for dilution which is different. This information is presented in a manner that may be confusing to practitioners when they refer to this panel for instruction.

#### ***4.2.3 Package insert***

Treanda was approved March 20, 2008 with the chronic lymphocytic leukemia indication and a recommended dose of 100 mg/m<sup>2</sup> to be infused over 30 minutes. The new indication of indolent B-cell non-Hodgkin's Lymphoma requires a dose of 120 mg/m<sup>2</sup> infused over 60 minutes. Because healthcare practitioners have become accustomed to the infusion rate of the previous indication, we anticipate errors between the two different rates.

Healthcare practitioners will benefit from education on the different rates of infusion in addition to the dosing. Various forms of education, chosen by the applicant, to ensure that healthcare providers are informed of the infusion rate changes may help remedy this confusion upon introduction of the new dose and rate.