CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

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:	March 18, 2008
To:	Robert Justice, MD Director, Division of Drug Oncology Products, HFD-150
Thru:	Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention
From:	Kristina C. Arnwine, PharmD, Acting Team Leader Division of Medication Error Prevention
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name:	Treanda (Bendamustine Hydrochloride) for Injection, 100 mg
Application Type/Number:	NDA # 22-249
Applicant/sponsor:	Cephalon, Inc
OSE RCM #:	2007-2064

CONTENTS

1 INTRODUCTION

This memo is written in response to a request from the Division of Drug Oncology Products (HFD-150), for clarification with regard to a typographical error in OSE 2007-2064.

2 MATERIAL REVIEWED

OSE review 2007-2064, dated March 10, 2008.

3 DISCUSSION

We note that Appendix D entitled "Products with no numerical overlap in strength and dose" contains the incorrect established name for the proposed product, Treanda. Appendix D lists the established name as "(choline fenofibrate)", rather than the correct established name "(bendamustine hydrochloride)". However, all of the information in Appendix D pertaining to Treanda is based on the established name bendamustine hydrochloride. Please see the revised appendix below.

4 CONCLUSIONS

In Appendix D, the correct established name for the proposed product, Treanda, should read "(bendamustine hydrochloride)".

If you have any questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at (301) 796-0675.

Appendix D: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Treanda (Bendamustine Hydrochloride)		**100 mg**	**Usual dose: 100 mg/m^2 given on days 1 and 2 of a 28-day cycle**
Trental	Look and Sound	400 mg	One tablet by mouth three times daily with meals
Trionate	Look	60 mg/5 mg	One tablet by mouth twice daily
Trinate	Look	Prenatal Multi-vitamin	One tablet by mouth once daily
Tripedia	Look	6.7 Lf/ 46.8 mcg/ 5 Lf/ 0.5 mL	0.5 ml as a 5-dose series in infants and children 6 weeks to 7 years of age.
Triant HC	Look	2 mg/1.67 mg/5 mg	1 teaspoonful to 2 teaspoonsful by mouth every 4 to 6 to 8 hours as needed
Ziana	Sound	1.2/0.025% gel	Apply topically to affected area at bedtime
Trientine	Sound	250 mg	750 mg to 1250 mg by mouth per day in 2 to 4 divided doses

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/s/

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3/18/2008 04:52:01 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/18/2008 04:54:24 PM
DRUG SAFETY OFFICE REVIEWER

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:	March 6, 2008
To:	Robert Justice, MD Director, Division of Drug Oncology Products, HFD-150
Thru:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention
From:	Kristina C. Arnwine, PharmD, Acting Team Leader Tselaine Jones-Smith, PharmD, Safety Evaluator Division of Medication Error Prevention
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name:	Treanda (Bendamustine Hydrochloride) for Injection, 100 mg
Application Type/Number:	NDA # 22-249
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OSE RCM #:	2007-2064

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

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Treanda, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we have no objection to the use of the proprietary name Treanda for this product. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the sponsor.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors. Improvements should be made to the container label, carton and package insert labeling to increase readability of information presented on the labeling. Such improvements include including a "discard — statement and the final milligram per milliliter concentration after reconstitution on the labels and labeling, as well as eliminating the use of the abbreviation — in the package insert labeling.

DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

This is considered a final decision. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product; we rescind this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, if 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 the signature date of this document.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Drug Oncology Products (HFD-150), for assessment of the proprietary name, Treanda, regarding potential name confusion with other proprietary or established drug names. The sponsor also submitted container labels, carton labeling, and package insert labeling for review and comment.

1.2 PRODUCT INFORMATION

Treanda is an antineoplastic agent indicated for the treatment of patients with chronic lymphocytic leukemia. Treanda must be diluted and prepared prior to use. The recommended dose is 100 mg/m^2 administered by intravenous infusion over 30 minutes on Days 1 and 2 of a 28-day cycle, for up to 6 cycles. Treanda will be supplied as single-use 20 mL vials containing 100 mg of bendamustine hydrochloride.

2 METHODS AND MATERIALS

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Treanda, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Treanda, our medication error staff searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the

proposed proprietary name (see 2.1.2). We also conduct internal CDER prescription analysis studies (see 2. 2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.3).

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 (see detail 2.3). 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. [1] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We define 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. [2] 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 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. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since 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 drug name include, but are not limited to established name of the proposed product, the proposed indication, 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, we consider 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.[3]

2.1 SEARCH CRITERIA

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'T' 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.[4][5]

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

[2] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

To identify drug names that may look similar to Treanda, the Staff also consider the other 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 'd'), downstrokes (none), cross-strokes (none), and dotted letters (none). Additionally, several letters in Treanda may be vulnerable to ambiguity when scripted, including the letter 'T' may appear as 'F'; lower case 'r' may appear as a lower case 's', 'a' or 'n'; lower case 'e' may appear as 'a' or 'i'; lower case 'a' may appear as 'r,' 'e,' or 's'; lower case 'n' may appear as 'r' or 's'; and 'da' may appear as 'do', 'cla', or 'clo'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Treanda.

When searching to identify potential names that may sound similar to Treanda, the Medication Error Staff search for names with similar number of syllables (three), stresses (Tre-AN-da, TRE-an-da, or Tre-an-DA), and placement of vowel and consonant sounds. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Treanda), the established name (bendamustine hydrochloride), proposed indication (chronic lymphocytic leukemia), strength (100 mg), dose (100 mg/m^2), frequency of administration (Days 1 and 2 of a 28-day cycle, up to 6 cycles), route (intravenous) and dosage form of the product (for injection). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed 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. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1 Data base and information sources

The proposed proprietary name, Treanda, was provided to the medication error staff to conduct a search 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 Treanda using the criteria outlined in 2.1. A standard description of the databases used in the searches is provided in Appendix A. To complement the process, the Medication Error 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 Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held to gather CDER professional opinions on the safety of the product and the proprietary name, Treanda. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

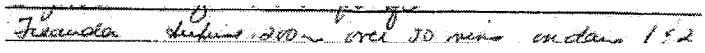
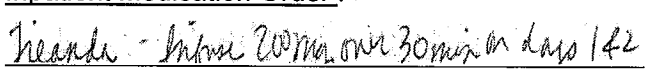
The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results,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

2.2 CDER 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 Treanda 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 a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Treanda in handwriting and verbal communication of the name, inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 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 the medication error staff.

Figure 1. Treanda Study (conducted on May 5, 2007)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Prescription #1: 	Treanda, infuse 200 mg over 30 minutes on Days 1 and 2.
Inpatient Medication Order : 	

2.3 SAFETY EVALUATOR RISK ASSESSMENT OF THE PROPOSED PROPRIETARY NAME

Based on the criteria set forth in Section 2.1.1, 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. 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, the Medication Error Prevention staff seeks to evaluate the potential for a proposed 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

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

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 then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product 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 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 evaluation, and studies, and identifies potential failure modes by asking: "Is the name Treanda convincing 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 Treanda 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 posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated 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 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, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

We will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. 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 trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify 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)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. 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.

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

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

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.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe 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 limitations of the process).

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.4 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 labels 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.[7]

Because the staff analyzes reported misuse of drugs, we 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 Sponsor submitted on September 20, 2007 the following labels and insert labeling for our review (see Appendix F and G for images):

- Container: 100 mg vial
- Carton
- Prescribing Information

Additionally, on February 20, 2008, the Division forwarded a working draft of the package insert that reflects all of the Division's revisions to the package insert to date.

3 RESULTS

3.1 DATA BASE AND INFORMATION SOURCES

Our search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug 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 settings identified twelve names as having some similarity to the name Treanda.

Seven of the twelve names were thought to look like Treanda, which include: Trecator, Namenda, Truvada, [redacted], Trionate, Trinate, and Tripedia.

Two names were thought to sound similar to Treanda: Ziana and Trientine.

Three names were thought to have look and sound similar to Treanda: Trandate, Trental, and Trendar

None of the twelve names contained a U.S. Adopted Name (USAN) stem.

3.1.1 CDER Expert panel discussion

The Expert Panel reviewed the pool of names identified by the medication error staff (see section 3.1.1. above), and noted one additional name, Triant HC, as having both orthographic and phonetic similarity to Treanda.

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

3.2 CDER PRESCRIPTION ANALYSIS STUDIES

A total of 31 practitioners responded, and none of the responses overlapped with any existing or proposed drug names. About half of the participants (n=16) interpreted the name correctly as "Treanda," with correct interpretation occurring more frequently in the written studies. The remainder of the responses

[7] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

misinterpreted the drug name. The majority of misinterpretations occurred in the second written prescription study, with the letter 'T' in Treanda reported as 'F' by 12 respondents. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.3 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look or sound similar to Treanda or represent a potential source of drug name confusion. As such, a total of 13 names were analyzed to determine if the drug names could be confused with Treanda and if the drug name confusion would likely result in a medication error.

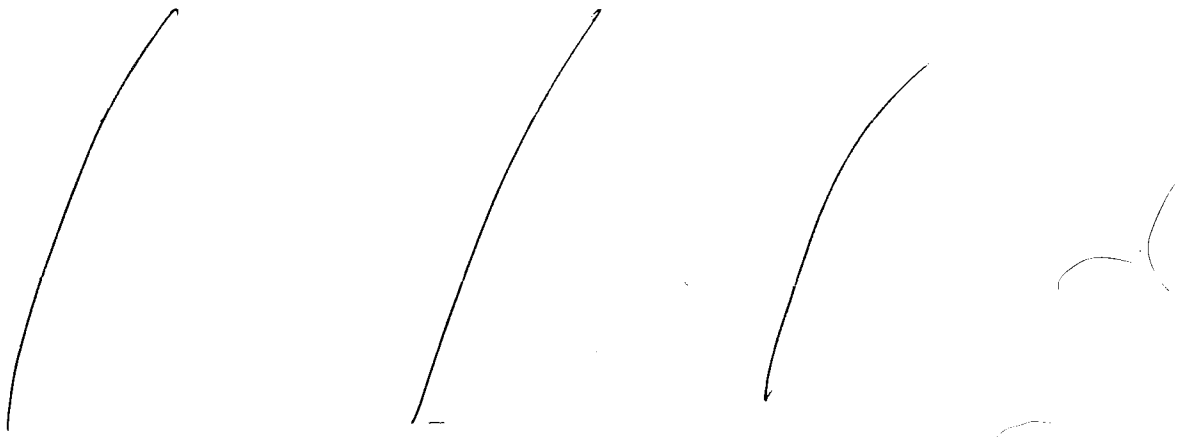
All of the identified names were determined to have some orthographic and/or phonetic similarity to Treanda, and thus determined to present some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name, Treanda, could potentially be confused with any of the 13 names and lead to medication error.

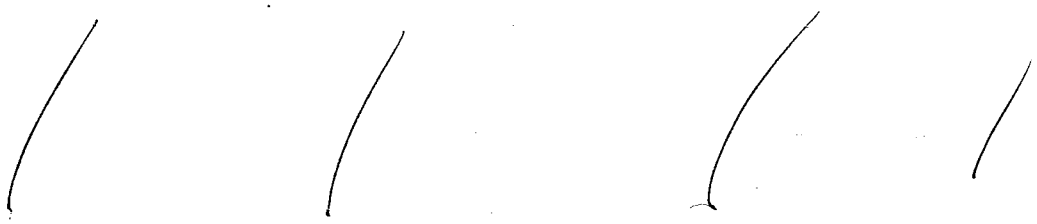
This analysis determined that the name similarity between Treanda and the identified names was unlikely to result in medication errors for all 13 products. One product (———) was a proposed proprietary name for another product within the Agency, however the sponsor withdrew the name and subsequently submitted a different proposed name for that product and thus was determined by FMEA to pose a minimal risk of error in usual practice setting (Appendix C).

For seven of the thirteen names identified, FMEA determined that medication errors were unlikely because the products do not overlap in strength or dosage with Treanda and have minimal orthographic and/or phonetic similarity to Treanda (Appendix D). The strength or dosage of the product most likely will be included in written and verbal prescriptions under typical conditions of practice which we determined will help to differentiate the products in combination with minimal similarity in appearance of these name pairs.

Five names (Trecator, Namenda, Truvada, Trandate, and Trendar) had some numerical overlap with Treanda in either dosage or strength, but analysis of the failure mode did not determine the effect of this similarity to result in medication errors in the usual practice setting (see Appendix E).

3.4 LABEL AND LABELING RISK ASSESSMENT





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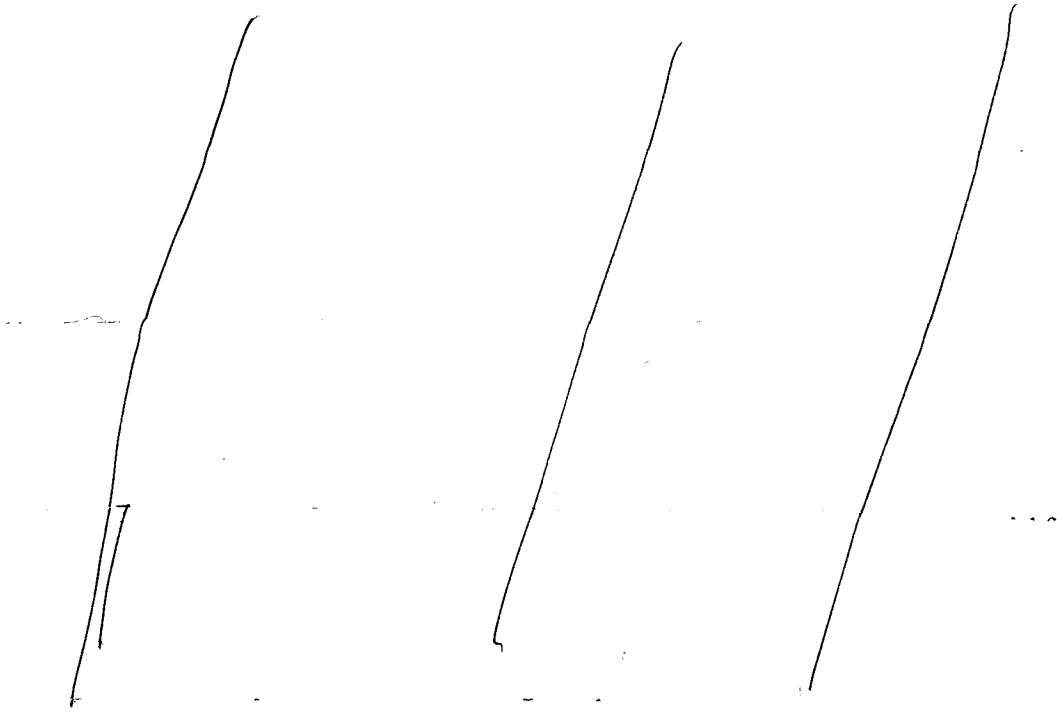
4 DISCUSSION

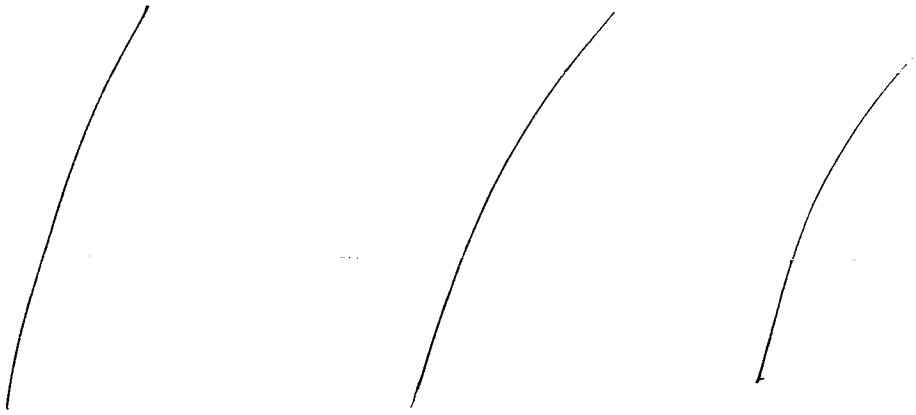
The results of the Proprietary Name Risk Assessment found that the proposed name, Treanda, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. Thus, we have no objections to the use of the proprietary name, Treanda, for this product.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, we believe that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Sponsor from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, we recommend that the proprietary name be re-submitted for review if the signature date of the NDA is delayed beyond 90 days.

The results of the Label and Labeling Risk Assessment





Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

The Proprietary Name Risk Assessment findings indicate that the proposed name, Treanda, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, we have no objections to the use of the proprietary name, Treanda, for this product. However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product; we rescind this Risk Assessment finding, and recommends that the name 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. This is considered a final decision. However, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

Based upon our assessment of the container labels and carton labeling submitted September 20, 2007 and the working draft revised package insert forwarded by the Division on February 27, 2008, we have identified areas of needed improvement, listed in section 5.2 below. We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Janet Anderson, Project Manager, at 301-796-0675.

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6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://weblern/)

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

3. 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, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

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

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Error Prevention proprietary name consultation requests

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

7. 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. 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.

9. WWW location http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (http://weblern/)

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.

11. 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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (http://weblern/)

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

13. Stat!Ref (http://weblern/)

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.pharmacist.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:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare 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. The Medication Error Staff also examine 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* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

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		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Inpatient-Sample 1	Inpatient-Sample 2	Voice
Treanda	Treanda	Trianda
Treanda	Treanda	Treeanda
Treanda	Freanda	Trianda
Treanda	Treanda	Treanda
Treanda	Freanda	
Treanda	Feanda	
Treanda	Freanda	
Treanda	Freanda	
Treanda	Freanola or Freanda	
Treanda	Freanda	
Treanda	Freanda	
	Freanda	
	Treanda	
	Feanda	
	Freanda	
	Freanda	

Appendix C: Proposed proprietary names for products not approved or approved with another name.

Proprietary Name	Similarity to Treanda
[redacted]	Look

***These names are proprietary and confidential that should not be released to the public.**

Appendix D: Products with no numerical overlap in strength and dose.

Treanda (Choline Fenofibrate)		100 mg	Usual dose: 100 mg/m^2 given on days 1 and 2 of a 28-day cycle
Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength**	**Usual Dose (if applicable)**
Trental	Look and Sound	400 mg	One tablet by mouth three times daily with meals
Trionate	Look	60 mg/5 mg	One tablet by mouth twice daily
Trinate	Look	Prenatal Multi-vitamin	One tablet by mouth once daily
Tripedia	Look	6.7 Lf/ 46.8 mcg/ 5 Lf/ 0.5 mL	0.5 ml as a 5-dose series in infants and children 6 weeks to 7 years of age.
Triant HC	Look	2 mg/1.67 mg/5 mg	1 teaspoonful to 2 teaspoonsful by mouth every 4 to 6 to 8 hours as needed
Ziana	Sound	1.2/0.025% gel	Apply topically to affected area at bedtime
Trientine	Sound	250 mg	750 mg to 1250 mg by mouth per day in 2 to 4 divided doses

Appendix E: Potential confusing name with numerical overlap in strength or dose

Treanda ® (bendamustine hydrochloride)	**100 mg**	**Usual dose: 100 mg/m^2 given on days 1 and 2 of a 28-day cycle**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Truvada (emtricitabine and tenofovir) 200 mg/300 mg tablets	Similar spelling of names begin with 'Tr-' and end with 'da' Similar length of name (seven letters) Potential numerical overlap with '200'	Product characteristic differences minimize the likelihood of medication error in the usual practice setting. Dose and route of administration will be required for Treanda prescriptions. *Rationale:* The risk of medication error is minimized by product characteristic differences. Treanda is dosed based on body surface area, thus a desired dose or body surface area, must be included on prescription orders. Additionally since Treanda will most likely only be used on an inpatient basis, orders will most likely be included on a chemotherapy order form and include a route of administration. Furthermore, Treanda is given only on days 1 and 2 of a 28 day chemotherapy cycle. Conversely Truvada will most likely be used primarily on an outpatient basis and dosed once daily. Prescription orders for Truvada may not include a dose or a route of administration since Truvada is only available in one strength and one dosage form.
Namenda (Memantine) 5 mg, 10 mg tablets 2 mg/mL oral solution	Similar spelling (-nda) Numerical overlap in strengths (100 mg versus 10 mg). Overlap could be exacerbated if a trailing zero (e.g. 10.0) is included with Namenda 10 mg	Orthographic and phonetic differences in the names and product characteristic differences minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk of medication error is minimized by the orthographic and phonetic differences in the names along with differing product characteristics. The beginnings of each name differ orthographically and phonetically (Trea- vs Name) which help differentiate the names from one another. Usual practice would not typically involve the inclusion of trailing zeros, though medication errors have been linked to this dangerous habit. Numerous campaigns (JCAHO, ISMP, FDA) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error. Treanda is dosed based on body surface area, thus a desired dose or body surface area, must be included on prescription orders. Additionally since Treanda will most likely only be

		used on an inpatient basis, orders will most likely be included on a chemotherapy order form and include a route of administration. Furthermore, Treanda is given only on days 1 and 2 of a 28 day chemotherapy cycle. Conversely Namenda will most likely be used primarily on an outpatient basis and dosed once daily.
Trandate (labetalol) 100 mg, 200 mg and 300 mg tablets 5 mg/mL solution for injection	Orthographic similarities, Tr-, '-nda'. Numerical overlap (100 mg)	Orthographic differences in the names and differing product characteristics reduce the risk of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by the orthographic differences in the names. The letters –nda- which are shared by each name are presented in differing positions in each name (end of Treanda vs. middle of Trandate). Additionally, the cross-stroke of the letter 't' at the end of Trandate helps to differentiate the names from one another. Moreover, Trandate appears longer when scripted. The risk of medication errors is further reduced by the differing product characteristics. Treanda is dosed based on body surface area, thus a desired dose or body surface area, must be included on prescription orders. Additionally since Treanda will most likely only be used on an inpatient basis, orders will most likely be included on a chemotherapy order form and include a route of administration. Furthermore, Treanda is given only on days 1 and 2 of a 28 day chemotherapy cycle. Conversely, Trandate, if used on an inpatient basis and given intravenously, is dosed up to every 10 minutes up to a total dose of 300 mg. When taken orally, Trandate is dosed by mouth twice daily.

Trecator (trazodone) 50 mg, 100 mg, 150 mg, 300 mg	Orthographic similarities, Tre- Possible numerical overlap (100 mg and 150 mg)	Orthographic differences in the names and differing product characteristics reduce the risk of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by the orthographic differences in the names. The middle and ending portions each of name differ orthographically (-cator vs. anda). Additionally, Treactor appears longer when scripted. The risk of medication errors is further reduced by the differing product characteristics. Treanda is dosed based on body surface area, thus a desired dose or body surface area, must be included on prescription orders. Additionally since Treanda will most likely only be used on an inpatient basis, orders will most likely be included on a chemotherapy order form and include a route of administration. Furthermore, Treanda is given only on days 1 and 2 of a 28 day chemotherapy cycle. Conversely, Trecator is dosed by mouth two or three times daily.
Trendar (ibuprofen) 200 mg tablets	Orthographic similarities, Tre- and -nda- Possible numerical overlap (200 mg)	Product characteristics reduce the risk of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by the differing product characteristics. Treanda is a prescription product dosed based on body surface area, thus a desired dose or body surface area, must be included on prescription orders. Additionally since Treanda will most likely only be used on an inpatient basis, orders will most likely be included on a chemotherapy order form and include a route of administration. Furthermore, Treanda is given only on days 1 and 2 of a 28 day chemotherapy cycle. Conversely, Trendar is an over-the-counter product which is dosed by mouth three times daily to four times daily. It will most likely be used on an outpatient basis. If Trendar is ordered by prescription, the established name, ibuprofen, will most likely be used.

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