

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125293

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: July 28, 2010

To: Badrul Chowdhury, MD, PhD, Director
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Division of Medication Error Prevention and Analysis
(DMEPA)

From: Cathy A. Miller, MPH, BSN, Safety Evaluator *C.A. Miller 7/28/2010*
Division of Medication Error Prevention and Analysis
(DMEPA)

Subject: Proprietary Name, Label, and Labeling Review

Drug Name: Krystexxa (Pegloticase) Injection
Uricase Protein 8 mg/mL

Application Type/Number: BLA 0125293

Applicant: Savient Pharmaceuticals, Inc.

OSE RCM #: 2010-638 and 2010-640

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

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EXECUTIVE SUMMARY

This re-assessment of the proprietary name is written in response to a notification that Biologic License Application (BLA) 012593 may be approved within 90 days. The Division of Medication-Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Krystexxa, acceptable in OSE Review #2008-1886 dated January 5, 2009, and again in OSE Review #2009-163 dated June 23, 2009. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) did not have any concerns with the proposed name, Krystexxa, during the previous reviews, and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on December 2, 2008.

In addition to the proposed proprietary name, DMEPA evaluated the revised container labels and carton labeling that were submitted in response to the recommendations made in OSE Review #2008-1799 dated May 15, 2009. The Applicant incorporated some of DMEPA's recommendations. Our recommendation to revise the dilution statement on the principal display panel of the carton labeling and add the dilution statement to the fold-out carton labeling was not incorporated into the revisions, therefore, we have reiterated our recommendations in Section 4 below.

1 BACKGROUND

1.1 REGULATORY HISTORY

DMEPA found the proposed name, Krystexxa, acceptable in OSE Reviews #2008-1886 dated January 5, 2009 and #2009-163 dated June 23, 2009. On July 31, 2009, DAARP issued a Complete Response letter to the Applicant citing CMC issues including deficiencies with the drug substance manufacturing, facilities inspection, a request for safety updates with the product and a request for a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with the use of Krystexxa and major cardiac events.

In March 2010, the Office of New Drugs (OND) underwent organizational changes that realigned the Rheumatology staff of the Division of Anesthesia, Analgesia and Rheumatology (DAARP) to the Division of Pulmonary and Allergy Products and renamed them the Division of Pulmonary, Allergy and Rheumatology Products (DPARP). The biological license application (BLA) 0125293 for Krystexxa was moved under the DPARP at that time. On March 15, 2010, the Applicant responded to the deficiencies cited in DPARP's Complete Response letter, along with revised container labels and carton labeling for review.

1.2 PRODUCT INFORMATION

Krystexxa (Pegloticase) infusion is a bio-uricolytic agent indicated for adult patients for the treatment of chronic gout in patients refractory to conventional therapy. Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia. Krystexxa is administered as an 8 mg dose administered by intravenous infusion every two weeks.

Krystexxa is available as a 1 milliliter sterile concentrate for dilution in a single-use 2 milliliter glass vial, containing 8 mg of Uricase protein per milliliter. Krystexxa should be mixed with 250 mL of 0.9 % Sodium Chloride Injection, USP or 0.45 Sodium Chloride Injection, USP for

intravenous infusion. Prior to administration, the admixture should be allowed to reach room temperature and should not be mixed with other drugs. Krystexxa should be only administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump and should not be administered as an intravenous push or bolus. If administration is delayed for any reason, it is recommended that diluted solutions be stored under refrigeration. Admixed solutions are stable at 2° to 8 ° C (36° to 46° F) and room temperature (68 ° to 77 ° F, 20° to 25 ° C) for 72 hours.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA for the final review of the proposed proprietary name, Krystexxa in Section 2.1, along with the proposed container labels and carton labeling in Section 2.2.

2.1 PROPRIETARY NAME

Since the proposed proprietary name “Krystexxa” has already been evaluated for this product, DMEPA staff search a standard set of databases and information sources (see Section 5) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We used the same search criteria outlined in OSE Review #2008-1886 dated January 5, 2009 and OSE Review #2009-163 dated June 23, 2009, for the proposed proprietary name, Krystexxa.

Since the last review of the proposed proprietary name, none of Krystexxa’s product characteristics have been altered. Thus, we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

2.2 LABELS AND LABELING

The Applicant submitted revised container labels (Appendix A) and carton labeling (see Appendix B and C) on March 15, 2010. DMEPA used Human Factors and Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the labels and labeling. We also evaluated the recommendations pertaining to the label and labeling presented in OSE review #2008-1799, dated May 15, 2009, to see if the DMEPA recommendations had been incorporated into the labels and labeling.

3 RESULTS

This section describes DMEPA’s evaluation of the proprietary name review in Section 3.1, along with the labels and labeling review in Section 3.2.

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

3.1 PROPRIETARY NAME

The searches of the databases did not yield any new names that were thought to look or sound similar to Krystexxa and represent a potential source of drug name confusion. Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of July 28, 2010.

3.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis reviewed the revised container labels and carton labeling and found that the recommendations we provided in OSE review #2008-1799 regarding the dilution statement had not been incorporated into the revised Krystexxa labels and labeling. As indicated in our previous review, the dilution statement, "Dilute Before Administration", that appears on the principal display panel of the outer carton labeling, is typically presented as "Must be Diluted Prior to Administration" for intravenous drug products requiring dilution before administration. During our initial labeling review, OSE Review #2008-1799 dated May 15, 2009, DMEPA consulted with the DPARP Review Team on the Application's selected language "Dilute Before Administration" and they concurred with our assessment that, in order to provide consistency in labeling, the statement should be presented as "Must Be Diluted Prior to Administration".

Additionally, the container label and the fold-out carton labeling that the Krystexxa vial is packaged inside do not contain the dilution statement that appears on the principal display panel of outer carton labeling. DMEPA understands that limited space on the container label may make it difficult to add the dilution language, however, we believe that adding the dilution statement to the principal display panel of the fold-out carton labeling that the vial is packaged inside may help to minimize the risk of maladministration of the drug.

DPARP's Complete Response letter to the Applicant dated July 31, 2009 included a requirement to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) to include a Medication Guide. DMEPA notes that the revised labels and labeling submitted by the Applicant include the addition of the language "Dispense the enclosed Medication Guide to each patient" on the principal display panel of the carton labeling. DMEPA is satisfied that this language adequately alerts healthcare practitioners to dispense a Medication Guide along with the medication.

4 CONCLUSIONS AND RECOMMENDATIONS

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

DMEPA has the following recommendations for revisions to the Krystexxa carton labeling and fold-out carton labeling, as originally cited in our OSE Review #2008-1799 dated May 15, 2009:

1. Revise the dilution statement that appears on principal display panel of the carton labeling to read "Must Be Diluted Prior to Administration" rather than the current presentation "Dilute Before Administration".

2. Add the dilution statement “Must Be Diluted Prior to Administration” to the fold-out carton labeling and if space permits, add the statement to the container label.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Pulmonary, Allergy and Rheumatology should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

We are willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carolyn Volpe, OSE project manager, at 301-796-5204.

5 REFERENCES

1. Miller, C. OSE Review #2008-1886: Proprietary Name Review for Krystexxa. January 5, 2009.
2. Miller, C. OSE Review #2009-163: Final Proprietary Name Review for Krystexxa June 23, 2009.
3. Miller, C. OSE Review #2008-1799: Label and Labeling Review for Krystexxa (Pegloticase) May 15, 2009.
4. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

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

USAN Stems List contains all the recognized USAN stems.

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

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



**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: June 24, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology

Through: Kellie Taylor, PharmD, MPH, Team Leader *Kellie Taylor 6/29/09*
Denise Toyer, PharmD, Deputy Director *D.P. Toyer 6/29/09*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Krystexxa (Pegloticase) for Intravenous Infusion
8 mg Uricase Protein/mL

Application Type/Number: BLA 125293

Applicant/Applicant: Savient Pharmaceuticals, Inc.

OSE RCM #: 2009-163

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EXECUTIVE SUMMARY

This re-assessment of the proprietary name is written in response to a notification that Biologic License Application (BLA 12593) may be approved within 90 days. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Krystexxa, acceptable in OSE Review# 2008-1886 completed January 5, 2009. Since that review, none of the Krystexxa product characteristics have changed that would alter the decision of acceptability from a promotional or safety perspective.

During this re-review we identified three new names for their similarity to Krystexxa. The results of the Failure Mode Effects Analysis found that the proposed name, Krystexxa, is not vulnerable to name confusion that could lead to medication errors with any of the three names. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Krystexxa, for this product.

DMEPA considers this a final review, however, if approval of the ^{BLA}~~NDA~~ is delayed beyond 90 days from the date of this review, the Division of Anesthesia, Analgesia and Rheumatology should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

1 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a re-assessment of a proprietary name 90 days prior to approval of an application. Section 1.1 identifies the specific search criteria associated with the proposed proprietary name, (b) (4).

1.1 SEARCH CRITERIA

For this review, DMEPA used the same search criteria used in OSE Review# 2008-1886. Please refer to Section 2.1.1 Page 4 of that review for the search criteria.

2 RESULTS

2.1 DATABASE AND INFORMATION SOURCES

The searches of the databases listed in Section 5 yielded a total of two names as having some similarity to the name Krystexxa. One name, Kristalose, was thought to look like Krystexxa, and the other name, (b) (4), was thought to sound like Krystexxa.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of May 15, 2009.

2.2 EXPERT PANEL DISCUSSION

The Expert Panel, as described in Appendix A reviewed the pool of names identified by DMEPA staff (See Section 2.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Krystexxa.

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

2.3 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in one additional name, Regranex, which was thought to look similar to Krystexxa and represent a potential source of drug name confusion.

Fifteen names (See Appendix B) were identified in the previous Krystexxa proprietary name review. None of the Krystexxa product characteristics have changed since the previous review. Therefore, the original assessment is maintained. Please see OSE #2008-1886 for a detailed analysis of these names.

3 DISCUSSION

Three new names were evaluated for their potential similarity to the proposed name, Krystexxa. Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the three names and lead to medication errors. This analysis determined that the name similarity between Krystexxa was unlikely to result in medication errors with any of the three products for the reasons presented in Appendices C and D. Additionally, DDMAC did not identify any issues with the proposed name, Krystexxa, from a promotional perspective.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Krystexxa, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Krystexxa, for this product at this time.

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

If you have further questions or need clarifications, please contact Chris Wheeler, Project Manager, at 301-796-0151.

5 REFERENCES

5.1 PREVIOUS OSE REVIEWS

OSE Review #2008-1886 dated January 5, 2009.

5.2 DATABASES

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

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

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

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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.

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

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

4. *AMF Decision Support System [DSS]*

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

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

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

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

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

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

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

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

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

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

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

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

Stat!Ref contains full-text information from approximately 30 texts; it 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.

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

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name.

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

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units,

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

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

recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³ DMEPA provides the product characteristics considered for this review in section one.

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

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

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

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

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

1. Database and Information Sources

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

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

2. CDER Expert Panel Discussion

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

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

3. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

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

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

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

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

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

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

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

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

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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

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

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

predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

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

Appendix B: Names previously reviewed and determined not to pose a safety risk.

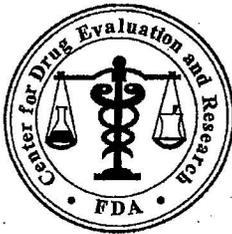
NAMES	
Byetta	Kristalose
Celexa	Pioglitazone
Cryselle	Ranexa
(b) (4)	Resistex
Cyclessa	Rynatuss
Cytoxan	Strattera
Euflexxa	Zyprexa
Histex HC	

Appendix C: Products with no numerical overlap in strength, dose and route of administration

Product name with potential for confusion	Similarity to Krystexxa	Strength	Usual Dose
Krystexxa		8 mg/mL	8 mg infused intravenously over 120 minutes
Kristalose	LA	10 gram/packet 20 gram/packet	10 grams to 20 grams daily

Appendix D: Products with potential numeric overlap in dose but multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Krystexxa	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics
Krystexxa		8 mg/mL	8 mg infused intravenously over 120 minutes	Dosage Form: Solution for injection Route of Administration: Intravenous Dose Expressed in milligrams
Kreteks	SA	1 % or 5 % Oil Extract 15 % Fluid (Tincture)	Oil Extract: 1 drop to 5 drops daily as needed Fluid Extract: 5 drops to 30 drops as needed	Dosage Form: Solution (oil) Route of Administration: Topical Dose expressed as “Apply ‘X’ drops”
Regranex	LA	100 mcg/gram (15 gram tube or 2 gram tube)	Apply topical to ulcer based on ulcer size calculation: (length X width X 0.6) for 15 gram tube (length X width X 1.3) for 2 gram tube	Dosage Form: Gel Route of Administration: Topical Dose expressed ‘apply topically’ or ‘apply gel topically’ along with ‘X’ centimeters or inches of gel.



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: January 5, 2009

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products

Through: Kellie Taylor, Pharm.D., M.P.H., Team Leader *Kellie Taylor 1/5/09*
Denise Toyer, Pharm.D., Deputy Director *DP. Toyer 1/5/09*
Carol Holquist, R.Ph., Director *Carol Holquist 1/5/09*
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, M.P.H., *Cathy Miller 1/5/09*
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Krystexxa (Pegloticase) for IV Infusion
8 mg Uricase Protein/mL

Application Type/Number: BLA 125293

Applicant: Savient Pharmaceuticals, Inc.

OSE RCM #: 2008-1886

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

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Krystexxa, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name Krystexxa, for this product. However, we note that the dosage form following the established name is presented as "For IV Infusion" instead of the labeling dosage form "For Intravenous Infusion". This should be revised prior to approval.

A re-review of the name prior to BLA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Applicant, Savient Pharmaceuticals, Inc., on November 14, 2008, for the proprietary name review of the proposed name, Krystexxa for the potential to contribute to medication errors. The Applicant also submitted container labels and carton labeling for review, which will be reviewed separately in our OSE Review #2008-1799.

1.2 REGULATORY HISTORY

Krystexxa (Pegloticase), received Ophan Drug Designation (00-1356)** in the United States on February 21, 2001 for the treatment of controlling clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective. On December 12, 2001, the Applicant submitted their Investigational New Drug (IND 10-122) for Pegloticase and on October 2, 2007, the Applicant submitted the proposed name, (b) (4), for review. On April 24, 2008, the Division of Medication Error Prevention and Analysis completed review OSE 2008-148 of proposed tradename, (b) (4), and found the name acceptable. On October 31, 2008, the Applicant submitted their Biological Licensing Application for Pegloticase and on November 14, 2008 submitted their request for review of the proposed tradename, Krystexxa, as their preferred proprietary name.

1.3 PRODUCT INFORMATION

Krystexxa (Pegloticase) is a bio-uricolytic agent indicated for adult patients for treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout. Krystexxa dose is 8 mg given intravenously every two weeks (b) (4),

Krystexxa is available as a 1 milliliter (mL) sterile concentration for dilution in a single-use 2 mL glass vial, containing 8 mg of Uricase Protein/mL for intravenous infusion.

Krystexxa should be mixed with 250 mL of 0.9 % Sodium Chloride Injection, USP 0.45 Sodium Chloride Injection, USP for intravenous infusion. Prior to administration, the admixture should be allowed to reach room temperature and should not be mixed with other drugs. Krystexxa should be only administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. Krystexxa should not be administered as an intravenous push or bolus. If administration is delayed for any reason, it is recommended that diluted solutions be stored under refrigeration. Admixed solutions of Krystexxa are stable at 2° to 8 ° C (36° to 46 ° F) and room temperature (68 ° to 77 ° F, 20° to 25 ° C) for 72 hours.

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' medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name 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.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Krystexxa, the medication error staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Section 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 2.1.1.2). We also conducted internal CDER prescription analysis studies (see 2.1.2). When provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment, however, there were no external prescription analysis studies provided for this application.

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 2.1.4). The overall risk assessment is based on the findings of a Failure Mode 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.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed

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

² Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

name could cause confusion that subsequently leads to medication errors in the clinical setting. 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

2.1.1 Search Criteria

The medication error prevention staff considers 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 'K' 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}

To identify drug names that may look similar to Krystexxa, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), capital letters ('K'), down strokes ('y'), upstrokes (capital letter 'K', and 't'), cross-strokes ('t' and 'x') and dotted letters (none).

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. Artificial Intelligence in Medicine (2005)

Additionally, several letters in Krystexxa may be vulnerable to ambiguity when scripted, including the capital letter 'K' may appear as capital letter 'R' or 'B'; lower case 'r' may appear as a lower case 'n', 'v' or 'u'; lower case letter 'y' may appear as lower case 'g', 'z' or 'j'; lower case 's' may appear as 'r' or 'a'; lower case 't' may appear lower case 'l', 'i' or 'r'; lower case 'e' may appear as lower case 'l', 'r' or 'i'; lower case 'x' may appear as lower case 'r', 'u', or 's'; and lower case 'a' may appear as lower case 'o', 'c' or 's'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Krystexxa.

When searching to identify potential names that may sound similar to Krystexxa, the medication error staff search for names with similar number of syllables (3), stresses (Krys-TEX-a and KRYS-tex-a), and placement of vowel and consonant sounds. In addition, certain letters in Krystexxa may be subject to misinterpretation when spoken, including the letter 'y' may be interpreted as either a hard or soft 'i' sound. The Applicant'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 (Krystexxa), the established name (Pegloticase), proposed indication (treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout), strength (8 mg of Uricase Protein in 1 mL), dose (8 mg), frequency of administration (every two (b) (4) weeks), route (intravenous infusion) and dosage form (solution for intravenous infusion). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

Lastly, the medication error staff also considers 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 provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Krystexxa, 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 Krystexxa using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the medication error staff uses 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.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the medication error and prevention staff to gather CDER professional opinions on the safety of the product and the proprietary name, Krystexxa. 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. As part of the Expert Panel Discussion, the group also provides handwriting samples of the proposed proprietary name along with other look-alike names identified by the panel and the Reviewing Safety Officer.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Krystexxa 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 Krystexxa 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. Since this medication is only administered in a clinically supervised inpatient setting, no outpatient medication orders were provided for this study. 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. Study (conducted on December 16, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order #1:</u></p> <hr/> <p><i>Krystexxa</i></p> <hr/> <p><i>Infuse 8 mg IV x 1 dose</i></p>	<p>Krystexxa Infuse 8 mg intravenously times one dose.</p>
<p><u>Inpatient Medication Order #2:</u></p> <hr/> <p><i>Krystexxa</i></p> <hr/> <p><i>Infuse 8 mg intravenously x 1 dose.</i></p>	

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

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 Mode 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 Division 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 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 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

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

Krystexxa convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Krystexxa to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system 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 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 identifies 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 Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, World Health Organization, Joint Commission on the Accreditation of Healthcare Organizations and the Institute for Safe Medication Practices, who 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 Applicant, 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 Applicant'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 Applicant 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 Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The Division of Medication Error Prevention and Analysis' searches identified fifteen names. Fourteen names with some similarity to the proprietary name, Krystexxa: Byetta, Celexa, Cryselle, (b) (4), Cyclessa, Cytoxan, Euflexxa, Histex HC, Kristalose, Ranexa, Resistex, Rynatuss, Strattera, and Zyprexa; and one name with some similarity to the established name Pegloticase: Pioglitazone.

Eight of the fifteen names were thought to look like Krystexxa: Byetta, Cryselle, Cyclessa, Cytoxan, Euflexxa, Resistex, Rynatuss and Strattera.

One of the fifteen names, Pioglitazone, was thought to look like the established name Pegloticase.

Five of the fifteen names was thought to sound like Krystexxa: Celexa, (b) (4), Histex HC, Ranexa, and Zyprexa.

One of the fifteen names, Kristalose, was thought to look and sound like Krystexxa

Additionally, the Division of Medication Error Prevention and Analysis did not identify any United States Adopted Names (USAN) stems in the name Krystexxa as of December 5, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the staff (see section 3.1.1. above) but did not identify any additional names with similarity to Krystexxa.

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

3.1.3 FDA Prescription Analysis Studies

A total of 26 practitioners responded to the FDA prescription analysis studies, but none of the responses overlapped with any existing or proposed drug names. Approximately fifty-seven percent (n=15) interpreted the name correctly as Krystexxa with correct interpretations only in the written studies. The remainder of the responses misinterpreted the drug name with misinterpretations occurring in both written and verbal studies. Misinterpretations include 'exxa' being misinterpreted as 'essa' (n=2), 'esso' (n=2), and 'exa' (n=5). See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment

3.1.4.1 Proprietary Name

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look or sound like Krystexxa. As such, a total of 15 names were

analyzed to determine if the drug names could be confused with Krystexxa 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 Krystexxa, and thus determined to present some risk of confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name Krystexxa could potentially be confused with any of the 15 names and lead to medication error. FMEA analysis determined that the name similarity between Krystexxa and the identified names was unlikely to result in medication error any of the 15 names. See Appendices C through I for our evaluation of the 15 names.

3.1.4.2 Presentation of the Dosage Form

We note that the dosage form following the established name is presented as “For IV Infusion” instead the labeling dosage form “For Intravenous Infusion”.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Fifteen names were evaluated for their potential similarity to the proposed name, Krystexxa. The FMEA of these names indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors in a clinical practice setting.

4.2 PRESENTATION OF THE DOSAGE FORM

We note that the dosage form following the established name is presented as “For IV Infusion” which uses the abbreviation “IV”. DMEPA contacted the Chemistry Reviewer for this application in the Office of Biotechnology Products, Division of Therapeutic Proteins who confirmed that the dosage form for biologic products such as Peglitocase is presented as “For Intravenous Infusion”, and therefore, the ‘IV’ in the proposed presentation should be spelled out as “Intravenous”.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Krystexxa, is not vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Krystexxa, for this product. Additionally, DDMAC does not object to the proposed name, Krystexxa, from a promotional perspective.

However, our assessment identified that the dosage form following the established name is presented as “For IV Infusion” instead of the Office of Biotechnology recommendation “For Intravenous Injection”. This should be addressed prior to approval.

5.1 COMMENTS TO THE DIVISION

5.1.1 Proprietary name:

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the applicant with regard to this review.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Krystexxa, and have concluded that it is acceptable.

The proprietary name, Krystexxa, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

Additionally, revise the presentation of the dosage form, spelling out the word intravenous, as follows:

(Pegloticase) For Intravenous Infusion

6 REFERENCES

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

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

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

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

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

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

4. *AMF Decision Support System [DSS]*

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

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

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

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

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. **Red Book Pharmacy's Fundamental Reference**

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

15. Lexi-Comp (www.lexi.com)

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication error staff considers 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 examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led 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 (e.g., "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 compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant 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
	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product	<ul style="list-style-type: none">Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communicationNames may look similar

Look-alike		characteristics	when scripted and lead to drug name confusion in written communication
	Orthographic similarity	<p>Similar spelling</p> <p>Length of the name</p> <p>Upstrokes</p> <p>Downstrokes</p> <p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: FDA Prescription Study Responses – Krystexxa

INPATIENT ORDER #2	INPATIENT ORDER #2	VOICE MESSAGE
Krystexxa	Krystessa	Cristexa
Krystexxa	Krystessa	Crystexa
Krystexxa	Krystesso	Cristexa
Krystexxa	Krystexxe	Cristexa
Krystexxa	Kujstesse	Crustexa
Krystexxa	Kuptesso	
Krystexxa		

Appendix C: Drug names lacking convincing look or sound-alike similarities to Krystexxa

Proprietary Name	Similarity to Krystexxa
Histex HC	Sound-Alike

Appendix D: Drug names not found in commonly referenced databases

Proprietary Name	Similarity to Krystexxa
Crystelle	Look-Alike

Appendix E: Drug names that are not approved products**

Proprietary Name	Similarity to Krystexxa	Status
		(b) (4)

Appendix F: Drug names that were past proposed proprietary names**

Proprietary Name	Similarity to Krystexxa	Status
Resistex	Look-Alike	Proposed name found unacceptable due to similarity with other marketed products and devices.

Appendix G Drug names with no numerical overlap in strength and dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Krystexxa (Pegloticase) for IV Infusion		8 mg Uricase Protein/mL supplied in a 2mL single-use vial.	8 mg given via intravenous infusion every two weeks (b) (4) [REDACTED]
Byetta (Exenatide Synthetic)	Look-Alike	300 UGM/1.2 mL (250 UGM/mL) Injectable 600 UGM/2.4 mL (250 UGM/mL) Injectable	5 mcg per dose administered subcutaneously twice daily at any time within sixty minute period before morning and evening meals. Dose may be increased to 10 mcg twice daily after one month therapy.
Celexa (Citalopram Hydrobromide)	Sound-Alike	10 mg, 20 mg, 40 mg, 60 mg Oral Tablets 10 mg/5 mL Oral Solution	20 mg once daily increased to a dose of 40 mg per day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week.
Cyclessa (Desogestrel and Ethinyl Estradiol)	Look-Alike	0.1 mg, 0.125 mg, 0.15 mg Oral Tablet 0.025 mg, 0.025 mg, 0.025 mg Oral Tablet	Take one tablet daily at the same time of day every day, at intervals not exceeding twenty-four hours.
*Cytosan (Cyclophosphamide) *Brand discontinued but generics available	Look-alike	25 mg and 50 mg Oral Tablets 500 mg/vial, 1 gram/vial and 2 gram/vial Injectable	40 mg/kg to 50 mg/kg intravenously in divided doses over a period of two to five days for treatment of malignant diseases or 10 mg/kg to 15 mg/kg given every seven to ten days or 3 mg/kg to 5 mg/kg twice weekly. 2.5 mg/kg to 3 mg/kg daily for sixty to 90 days for biopsy proven minimal change nephritic syndrome in children
Kristalose (Lactulose)	Look-Alike and Sound-Alike	10 gram/15 mL Solution 10 gram and 20 gram Powder for Solution	Oral Solution: Mix with full glass of water, milk, fruit juice or carbonated citrus beverage and administer orally on empty stomach. Powder: Dissolve contents of 10 gram or 20 gram package into at least four ounces of water and administer orally on empty stomach
Pioglitazone (Pioglitazone Hydrochloride)	Look-Alike (Pegloticase)	15 mg, 30 mg, and 45 mg Oral Tablets	Monotherapy or Combination Therapy: 15 mg or 30 mg once daily
Ranexa (Ranolazine)	Sound-Alike	500 mg and 1 gram Extended-Release Oral Tablets	500 mg twice daily and increase to 1000 mg twice daily as needed based on clinical symptoms
Zyprexa (Olanzapine)	Sound-Alike	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg Oral Tablets 10 mg/vial for Injection	Schizophrenia: 5 mg to 10 mg once a day initially, with a target dose of 10 mg per day. Bipolar Disorder: 5 mg to 10 mg once a day initially, dosage adjustment, if indicated at intervals of not less than twenty-four hours in increments of 5 mg per day. Maintenance dose of 5 mg to 20 mg per day. Agitation Associated with Schizophrenia and Bipolar 1 Mania: 2.5 mg to 10 mg intramuscular injection

Appendix H: Drug names with overlap strength and dose but multiple differentiating product characteristics

Product name with potential for confusion	Strength	Usual Dose (if applicable)	Differentiating Product Characteristics
Krystexxa (Pegloticase) for IV Infusion	8 mg Uricase Protein/mL supplied in a 2mL single-use vial.	8 mg given via intravenous infusion every two weeks (b) (4)	Dosage Form is solution for injection Route of Administration in intravenous injection One recommended dose
Strattera (Atomoxetine Hydrochloride)	5 mg, 110 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg Oral Capsules	Children up to 70 kg: 0.5 mg/kg initial dose; 1.2 mg/kg target daily dose in single dose or divided doses in morning and late afternoon Children and adults > 70 kg: 40 mg initial dose; target total daily dose 80 mg in single dose or divided doses in morning and late afternoon	Dosage Form is Oral Capsules Route of Administration is oral Multiple recommended doses

Appendix I: Drug names with potential for confusion due to single strength availability

Failure Mode: Name confusion	Causes (could be multiple)	Effect
Krystexxa (Pegloticase) for IV Infusion	8 mg Uricase Protein/mL supplied in a 2mL single-use vial.	8 mg given via intravenous infusion every two weeks (b) (4)
Euflexxa (1 % Sodium Hyaluronate) in 2.25 mL syringe	Orthographic similarities: 'r' can look like 'u'; 'texxa' looks like 'lexxa'.	Orthographic differences in names, route of administration, packaging, dose, and procedure for administration minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The downstroke 'y' in Krystexxa is not present in Euflexxa, differentiating the two drug name appearances. Euflexxa is packaged in a ready-to-use 2.25 mL prefilled syringe and is administered only by trained physician intra-articularly into the knee synovial capsule, with the dose measured in milliliters (give 2 mL per knee). Krystexxa is packaged in a 2 mL glass vial requiring dilution in 250 mL normal saline or half normal saline and then infused intravenously over 120 minutes, with the dose measured in milligrams (8 mg). Additionally, because Krystexxa is administered in a supervised clinical setting, the dose (8 mg) and route of administration (intravenous infusion) would be specified on physician orders, minimize the risk of medication error occurring.
Rynatuss (Carbetapentane,	Orthographic similarities: 'K' can look like	Orthographic differences in names, dosage form and route of

<p>Chlorpheniramine, Ephedrine and Phenylephrine) 60 mg-5 mg-10mg-10mg Oral Tablets</p>	<p>'R'; 'y' similarly positioned in both names; 't' similarly positioned in both names' 'xx' can look like 'ss' when scripted.</p>	<p>administration minimize the likelihood of medication error in the usual practice setting. <i>Rationale:</i> The 'y' is located in the third letter position of Krystexxa while it is located in the second letter position of Rynatuss. Additionally, there is an 'a' in the last letter position of Krystexxa not present in Rynatuss, which differentiates the appearances of the names. Though both products are available in only one strength, Rynatuss is available in tablet form administered orally while Krystexxa is an intravenous solution administered via intravenous infusion under medical supervision in a hospital, which would require physician orders specifying drug name, strength, dose and route of administration. This would minimize the risk of medication errors occurring between Krystexxa and Rynatuss.</p>
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