CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125293

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW-Amendment

Application Number: **STN 125293/0**

Name of Drug: **KRYSTEXXA™**

Sponsor: **Savient Pharmaceuticals, Inc.**

Material Reviewed: **KRYSTEXXA™ (pegloticase) Carton and Container Labels**
Patient Package Insert

OBP Receipt Date: **October 31, 2009, March 15, 2010**

EXECUTIVE SUMMARY

The carton and container labels for KRYSTEXXA™ (pegloticase)were reviewed and found to comply with the most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 12/1/09-10/1/10, USP 32/NF27. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background:

STN 125293/0 for pegloticase is an original Biologic License Application (BLA) indicated for the treatment of gout to control hyperuricemia and to manage the signs and symptoms of gout (b) (4) The product is supplied as an 8 mg mg/mL in a single use 2 mL glass vial and packaged to deliver 1 mL of drug for dilution. The product is a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous use only.

Labels Reviewed:

Krystexxa™ (pegloticase) Container Label
Vial label
Krystexxa™ (pegloticase) Carton Label

Carton peel off sticker
Carton label (outer)
Carton label (inner)
Krystexxa™ (pegloticase) Patient Package Insert
Product title line, Description, How supplied/Storage

Review

(b) (4)

[redacted]

1 Page of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)

[redacted]

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
   a. The proper name of the product, pegloticase is displayed along with the proprietary name KRYSTEXXA®. This conforms to the regulation.

   b. The name, addresses, and license number of the manufacturer – The address should be listed, along with the U.S. license number. "Savient Pharmaceuticals, Inc." is

listed without the US License number. This does not conform to the regulation.

c. The lot number or other lot identification – The lot number is not displayed on the container label. This conforms to the regulation. This does not conform to the regulation.

d. The expiration date – The expiration date is not displayed on the container label. This does not conform to the regulation.

e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial. This regulation does not apply.

f. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the label. This conforms to the regulation.

g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A medication guide statement is not displayed on the label. This does not conform to the regulation. Recommend placing statement on carton to conform to regulation due to size of the vial label.

2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This does not apply.

3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This does not apply.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted,

provided the container is placed in a package which bears all the items required for a package label. – This container bears a label. This does not apply.

5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located in the top 1/3 of the label. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. The NDC configuration appears as, "NDC XXXX-XXX-XX". This conforms to the regulation.

C. 21 CFR 201.5 Drugs; adequate directions for use – There is no reference to the prescribing information on the container label due to space limitations. The reference is displayed on the carton. This conforms to the regulation.

D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the trade name and proper name. This conforms to the regulation.

E. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is a specified biologic and is regulated 21 CFR 201.10. Prominence of the established name is incorrect. This does not conform to the regulation.

F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only") are prominent and do not overlap. This conforms to the regulation.

G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not listed on the label. This does not conform to 21 CFR 610.60 or 21 CFR 201.17.

H. 21 CFR 201.25 Bar code label requirements –A bar code is present of the label. This conforms to the regulation.

I. 21 CFR 201.50 Statement of identity – The proper name, pegloticase is stated on the label with the trade mark name KRYSTEXXA™. The prominence of the proper name does not comply with 21 CFR 201.10. This does not conform to the regulation.

J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is declared on the label as (b) (4). This declaration is incorrect. This does not conform to the regulation.

K. 21 CFR 201.55 Statement of dosage – A statement of dosage or a reference to the package insert is not displayed on the container label. Space limitations are an issue. This does not conform to the regulation. Recommend the statement appear on both cartons.

L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. The manufacturer information is not listed correctly. This does not conform to the regulation.

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

II. Carton

A. 21 CFR 610.61 Carton/Package Label – Outer (T022807CA) and (inner) (M021507DB)

a. The proper name of the product, pegloticase is displayed along with the proprietary name KRYSTEXXA® on both carton labels. This conforms to the regulation.

b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. Both cartons display, "Manufactured by
Sigma-Tau PharmaSource, Inc. for Savient
Pharmaceuticals, Inc.,
One Tower Center,
East Brunswick, NJ 08816" is listed with "US License no. 125293". Sigma-Tau is not listed as the applicant per 600.3(t) on the 356h. The BLA number is currently listed as the license number on the outer carton only. This does not conform to the regulation. Revise the manufacturer information on both and display the correct license number on both cartons.

c. The lot number or other lot identification – The lot number is not displayed on the inner carton, but is displayed on the outer carton. This does not conform to the regulation.

d. The expiration date – The expiration date is not displayed on the inner carton, but is not displayed on the outer carton. This does not conform to the regulation.

e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" –The statement "No Preservative" is not displayed on the carton. This does not conform to the regulation.

f. The number of containers, if more than one – The following statement appears on both cartons, "Single-dose vial". This conforms to the regulation. Recommend revising to "Single-use vial".

g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be

reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable - (b) (4) s t . This does not conform to the regulation.

h. The recommended storage temperature – The statement "Store in carton at 2°C - 8 °C (36°F - 46°F)." is displayed on the side panel of the outer carton. There are no storage conditions displayed on the inner carton. This does not conform to the regulation.

i. The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product – Revise to, "Do not shake or freeze" and add "Protect from light" to the carton labels. This does not conform to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –The product is supplied in a "single-dose vial". Not applicable.

k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement "FOR INTRAVENOUS INFUSION ONLY" is located on both cartons. This conforms to the regulation. Recommend revising format to upper and lowercase lettering and removing "only".

l. Known sensitizing substances, or reference to enclosed circular containing appropriate information – None present. This conforms to the regulation.

m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.

n. The inactive ingredients when a safety factor or reference to enclosed circular containing appropriate information. USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, the list of all inactive ingredients must be in alphabetical order. - Inactive ingredients are listed on the outer carton in alphabetical order, however a listing of inactive ingredients do not appear on the inner carton. This does not conform to the regulations.

o. The adjuvant, if present –None present. This conforms to the regulation.

p. The source of the product when a factor in safe administration –This conforms to the regulation.

q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – *E. coli* is not listed on either carton and does not appear in the Package insert. This does not conform to the regulation. Recommend adding the organism information to the cartons.

r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency" – "No U.S. Standard of Potency" is not displayed on either carton. This does not conform to the regulation.

s. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on both cartons. This conforms to the regulation.

t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A proposed medication guide has been submitted to the BLA however the required medication guide statement is not displayed on either carton. This does not conform to the regulation.

B. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This product is a "specified" biological product. The placement and prominence of the Proper and Tradename must comply with 21 CFR 201.10. This regulation does not apply.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown –This regulation does not apply.

D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated. –no distributor is listed. This regulation does not apply.

E. 21 CFR 610.65 Products for export – This is for US use only. This regulation does no apply.

F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on both carton labels. This conforms to the regulation.

G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the front panel of both cartons. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

H. 21 CFR 201.5 Drugs; adequate directions for use – The outer carton label states "See enclosed full prescribing information for dosage and administration." The inner carton does not have any reference to the package insert or - This does not conform to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the trademark and proper name. This conforms to the regulation.

J. 21 CFR 201.10 Drugs; statement of ingredients – Prominence of the proper name is incorrect. This does not conform to the regulation.

K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only") are prominent and do not overlap. This conforms to the regulation.

L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is displayed on the outer carton label and is not displayed on the inner carton. This does not conform to the regulation.

M. 21 CFR 201.25 Bar code label requirements – A Bar code is displayed on both the outer and inner carton labels. This conforms to the regulation.

N. 21 CFR 201.50 Statement of identity – The proper name, pegloticase is stated on the label with the trade mark name KRYSTEXXA™. The prominence of the proper name does not comply with the regulation. This does not conform to the regulation.

O. 21 CFR 201.51 Declaration of net quantity of contents –The net quantity of contents is declared on the label as (b) (4) This declaration is incorrect. This does not conform to the regulation.

P. 21 CFR 201.55 Statement of dosage – The outer carton label states "See enclosed full prescribing information for dosage and administration." The inner carton does not have any reference to the package insert. This does not conform to the regulation. Recommend the statement, "See package insert for dosage, dilution, and administration."

Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. The label does not indicate that the product is light sensitive, the manufacturer information is listed incorrectly, and required information does not appear. This does not conform to the regulation.

III. Conclusions

Revised labels and explanations submitted September 3, 2010 to the BLA.

A. Container label

1. Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Information provided in cover letter of submission dated September 3, 2010. Acceptable.

2. The license number does not appear on the vial label with manufacturer information. Please add the license number below the manufacturing information per 21 CFR 610.60(2). Per submission dated September 3, 2010, the license number presented on the label (BLA number 125293) is incorrect. The license number has been designated as 1801. Not acceptable. Revised label submitted September 13, 2010 are acceptable.

3. Please add the lot number and expiration date to the container label to comply with 21 CFR 610.60(c)(d). Per submission dated September 3, 2010 Expiration date in format mm/yyyy and lot number in four numeric characters will be laser etched on the purple tab on the right portion of the vial label. Acceptable.

B. Carton labels- Outer (T022807CA) and inner (M021507DB)

1. Please add a medication guide statement to read, "Dispense the enclosed Medication Guide to each patient." with prominence to comply with 21 CFR 610.60(7) and 21 CFR 208.24(d). Per submission dated September 3, 2010. Statement added. Acceptable.

2. Please add the statement "No U.S. standard of potency." to both carton labels to comply with 21 CFR 610.61(r). Per submission dated September 3, 2010, statement added. Acceptable.

3. Revise the active ingredient statement to read, [redacted] (b) (4) " followed by the inactive ingredient listing. Per submission dated September 3, 2010, statement revised Acceptable.

4. Under USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order. Per submission dated September 3, 2010, listing revised. Acceptable.

5. Please add the statement, "No Preservative" to both carton labels to comply with 21 CFR 610.61(e). Per submission dated September 3, 2010, statement added. Acceptable.

6. Please add the statement "Protect from light" and revise, "DO NOT FREEZE." to "Do not shake or freeze." to comply with 21 CFR 610.61(i). Per submission dated September 3, 2010, changes made. Acceptable.

7. Pleas revise the manufacturer information to comply with 21 CFR 601.3(k). The applicant must be listed as the manufacturer. Per submission dated September 3, 2010, information revised. Acceptable.

8. The inner carton (M021507DB) is considered an immediate carton and must comply with applicable package labeling requirements. The inner carton must contain the same information as the outer carton or it must be completely blank.
    a. The license number is not displayed with the manufacturer information. Please add the license number below the manufacturing information per 21 CFR 610.60(2).
    b. Please add the lot number and expiration date to comply with 21 CFR 601.61(c)(d) and 21 CFR 201.17.

c. Please add recommended storage conditions per 21 CFR 610.61 (h).

d. Please add a reference to the full prescribing information per 21 CFR 201.5 and 201.55.

Per submission dated September 3, 2010, the inner carton is blank except for the statement, "PUSH here gently to release vial". Acceptable.

C. Carton and Container Labels

1. Please revise the presentation of the Proprietary name, proper name, strength to:

KRYSTEXXA
(pegloticase)
Injection
8 mg/ mL
For Intravenous Infusion

Single-use vial. Discard unused portion
Must be diluted prior to use

Per submission dated September 3, 2010, statements added as requested. Acceptable.

2. Please revise the font size and prominence of the trade name (proprietary name) and proper name (established name) presentations to comply with 21 CFR 201.10(g)(2). The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing factors. Per submission dated September 3, 2010, the prominence of the strength and proper name (established name) are not acceptable. Decrease the prominence of the Trade name and increase the prominence and font size of the strength presentation and proper name (established name). Not acceptable. Revised labels submitted September 13, 2010 are acceptable.

Patient Package Insert comments:

1. Please revise the presentation from, [redacted] (b) (4) to "8 mg of pegloticase" in the DOSAGE FORMS & STRENGTHS, DESCRIPTION, and HOW SUPPLIED sections to provide an accurate representation of the strength of

the product per 21 CFR 201.57(c)(17) and 21 CFR 610.61(g) throughout the labeling. Changes made and acceptable.

2. Please add the established name, "(pegloticase)" immediately after the brand name "KRYSTEXXA" in the description section to comply with 21 CFR 201.57(c)(12). Changes made and acceptable.

3. Under USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order. Changes made and acceptable.

4. Please revise the abbreviation "i.v. infusion" to "intravenous infusion" in the" HOW SUPLLIED" section of the PPI to comply with the Institute for Safe Medication Practices "List of Error Prone Abbreviations, Symbols and Dose Designations." Changes made and acceptable.

5. Please add the bolded statement "Do not shake or freeze" to the "STORAGE AND HANDLING" section of the PPI per 21 CFR 201.57(c)(17)(iv). Changes made and acceptable.

Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP/IOD

Comment/Concurrence:

13 Sept 2010

Howard Anderson, Ph.D.
Product Reviewer
CDER/OPS/OBP/DTP

Barry Cherney, Ph. D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125293/0

Name of Drug: KRYSTEXXA™

Sponsor: Savient Pharmaceuticals, Inc.

Material Reviewed: KRYSTEXXA™ (pegloticase) Carton and Container Labels
Package Insert

OBP Receipt Date: October 31, 2009, March 15, 2010

EXECUTIVE SUMMARY

The carton and container labels for KRYSTEXXA™ (pegloticase)were reviewed and found to comply with the most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 12/1/09-10/1/10, USP 32/NF27. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background:

STN 125293/0 for pegloticase is an original Biologic License Application (BLA) indicated for the treatment of gout to control hyperuricemia and to manage the signs and symptoms of gou (b) (4) The product is supplied as an 8 mg mg/mL in a single use 2 mL glass vial and packaged to deliver 1 mL of drug for dilution. The product is a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous use only.

Labels Reviewed:

Krystexxa™ (pegloticase) Container Label
Vial label
Krystexxa™ (pegloticase) Carton Label

Carton peel off sticker
Carton label (outer)
Carton label (inner)
Krystexxa™ (pegloticase) Package Insert
Product title line, Description, How supplied/Storage

Review

(b) (4)

[redacted]

11 Page(s) of Draft Labeling have been Withheld in full immediately following this page as B4 (CCI/TS)

(b) (4)

[redacted]

III. Conclusions

A. Container label

1. Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e).

2. The license number does not appear on the vial label with manufacturer information. Please add the license number below the manufacturing information per 21 CFR 610.60(2).

3. Please add the lot number and expiration date to the container label to comply with 21 CFR 610.60(c)(d).

B. Carton labels- Outer (T022807CA) and inner (M021507DB)

1. Please add a medication guide statement to read, "Dispense the enclosed Medication Guide to each patient." with prominence to comply with 21 CFR 610.60(7) and 21 CFR 208.24(d).

2. Please add the statement "No U.S. standard of potency." to both carton labels to comply with 21 CFR 610.61(r).

3. Revise the active ingredient statement to read, "Each 8 mg/mL vial of pegloticase contains: 8 mg uricase protein covalently linked to 24 mg PEG" followed by the inactive ingredient listing.

4. Under USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order.

5. Please add the statement, "No Preservative" to both carton labels to comply with 21 CFR 610.61(e)

6. Please add the statement "Protect from light" and revise, "DO NOT FREEZE." to "Do not shake or freeze." to comply with 21 CFR 610.61(i).

7. Pleas revise the manufacturer information to comply with 21 CFR 601.3(k). The applicant must be listed as the manufacturer.

8. The inner carton (M021507DB) is considered an immediate carton and must comply with applicable package labeling requirements. The inner carton must contain the same information as the outer carton or it must be completely blank.
    a. The license number is not displayed with the manufacturer information. Please add the license number below the manufacturing information per 21 CFR 610.60(2).
    b. Please add the lot number and expiration date to comply with 21 CFR 601.61(c)(d) and 21 CFR 201.17.
    c. Please add recommended storage conditions per 21 CFR 610.61 (h).
    d. Please add a reference to the full prescribing information per 21 CFR 201.5 and 201.55.

C. Carton and Container Labels

1. Please revise the presentation of the Proprietary name, proper name, strength to:

    KRYSTEXXA
    (pegloticase)
    Injection
    8 mg/ mL
    For Intravenous Infusion

    Single-use vial. Discard unused portion
    Must be diluted prior to use

2. Please revise the font size and prominence of the trade name (proprietary name) and proper name (established name) presentations to comply with 21 CFR 201.10(g)(2). The

established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing factors.

Package Insert comments:

1. Please revise the presentation from, (b) (4) to "8 mg of pegloticase" in the DOSAGE FORMS & STRENGTHS, DESCRIPTION, and HOW SUPPLIED sections to provide an accurate representation of the strength of the product per 21 CFR 201.57(c)(17) and 21 CFR 610.61(g) throughout the labeling.

2. Please add the established name, "(pegloticase)" immediately after the brand name "KRYSTEXXA" in the description section to comply with 21 CFR 201.57(c)(12).

3. Under USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order.

4. Please revise the abbreviation "i.v. infusion" to "intravenous infusion" in the" HOW SUPLLIED" section of the PPI to comply with the Institute for Safe Medication Practices "List of Error Prone Abbreviations, Symbols and Dose Designations."

5. Please add the bolded statement "Do not shake or freeze" to the "STORAGE AND HANDLING" section of the PPI per 21 CFR 201.57(c)(17)(iv).

9/1/10

Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP/IOD

Comment/Concurrence:

28 Sept 2010

Howard Anderson, Ph.D.
Product Reviewer
CDER/OPS/OBP/DTP

Amy Rosenberg for Barry Cherney 9-2-10

Barry Cherney, Ph. D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

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:	August 30, 2010
To:	Badrul Chowdhury, MD, Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	Claudia Karwoski, Pharm D, Director 8/30/10 **Division of Risk Management (DRISK)**
	LaShawn Griffiths, RN, MSHS-PH, BSN Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Melissa Hulett, RN, BSN, MSBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling Medication Guide
Drug Name(s):	KRYSTEXXA (pegloticase) Injection for Intravenous Infusion
Application Type/Number:	BLA 125293
Applicant/sponsor:	Savient Pharmaceuticals, Inc.
OSE RCM #:	2010-633

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Krystexxa (pegloticase) Injection for Intravenous Infusion.

On October 31, 2008 Savient Pharmaceuticals, Inc. submitted BLA application 125293 for Krystexxa (pegloticase) Injection for Intravenous Infusion for the treatment of gout that had failed other treatments. On July 31, 2009 this product received a CR letter due to quality and facility deficiencies. A REMS with medication guide and communication plan were requested from Savient Pharmaceuticals, Inc to mitigate infusion reactions and to add a contraindication for patients with a G6PD deficiency. On March 15, 2010 Savient Pharmaceuticals, Inc. submitted their complete response to include the REMS, Medication Guide, and Communication Plan.

The proposed REMS is being reviewed by DRISK and will be provided to DPARP under separate cover.

2 MATERIAL REVIEWED

- Draft Krystexxa (pegloticase) Injection for Intravenous Infusion Prescribing Information (PI) submitted March 15, 2010 and revised by the Review Division throughout the current review cycle and received by DRISK on August 19, 2010.
- Draft Krystexxa (pegloticase) Injection for Intravenous Infusion Medication Guide (MG) submitted on March 15, 2010 and received by DRISK on August 19, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please send DRISK's comments to the Applicant and copy us on the correspondence. Let us know if DPARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

Please let us know if you have any questions.

20 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/ TS)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: August 25, 2010

To: Ramani Sista, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Twyla Thompson, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Kathleen Klemm, Regulatory Review Officer

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
(DDMAC)

Subject: BLA 125293
DDMAC draft labeling comments for KRYSTEXXA™ (pegloticase) Injection, for intravenous infusion

---

DDMAC has reviewed the revised proposed product labeling (PI) and revised proposed Medication Guide for KRYSTEXXA™ (pegloticase) Injection, for intravenous infusion (Krystexxa) submitted for consult on August 12, 2010. DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "BLA 125293 Krystexxa label FDA edits 8-20-10.doc" that was sent via email from DPARP to DDMAC on August 20, 2010. DDMAC's comments on the Medication Guide are based on the proposed draft marked-up labeling titled "medication-guide_031510.doc" that was sent via email from DPARP to DDMAC on August 19, 2010.

DDMAC's comments on the PI and Medication Guide are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on this label. If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Twyla Thompson at (301) 796-4294 or twyla.thompson@fda.hhs.gov.

21 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/ TS)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An observational safety study enrolling 500 patients treated with pegloticase for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid lowering therapies (e.g., allopurinol). The study should include the following objectives: 1) evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events; and 2) identify serious adverse events associated with pegloticase therapy.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	February 2011
	Study/Ttrial Completion:	July 2015
	Final Report Submission:	December 2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Due to the orphan indication and limited safety database available pre-approval, additional safety information should be obtained post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The clinical safety database identified infusion reactions and anaphylaxis as a safety issue. The study should include the following objectives: 1) evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events; and 2) identify serious adverse events associated with pegloticase therapy..

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational safety study enrolling 500 patients treated with pegloticase for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid lowering therapies (e.g., allopurinol).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Conduct a male and female fertility study in rats as per ICH S5A and ICH-S5B guidance

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	January 2011
	Study/Ttrial Completion:	November 2011
	Final Report Submission:	June 2012
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The applicant did not provide information on the mating performance in male and female animals. Data from histopathology of gonads are not adequate to extrapolate mating performance and early embryonic development.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Results of the study would provide non-clinical data on potential toxicity of pegloticase on early embryonic development and spontaneous abortion. [redacted] (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The recommended study is a non-clinical study where both male and female rats will be pretreated with pegloticase before mating and during mating so that effect of the treatment on early implantation and embryonic development could be determined.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Conduct an embryo-fetal development study in the rabbit model (segment 2) according to ICH-S5A guidance

PMR/PMC Schedule Milestones:

Final Protocol Submission:	September 2011
Study/Ttrial Completion:	March 2012
Final Report Submission:	September 2012
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The applicant did not provided information on the potential effect of pegloticase on organogenesis in a second species required according to the ICH guidelines.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Results of the study would provide non-clinical data on potential effects of pegloticase on fetal development in a second species. Currently the product is approved with a labeling statement on data obtained in rats only. The effect on another species is required for adequate non-clinical data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The recommended study is a non-clinical study where pregnant female rabbits will be treated with pegloticase during post-implantation and organ formation of the fetus so that effect of the treatment on embryonic development could be determined.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Conduct a peri-natal and post-natal development study in the rat model (Segment 3)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	January 2011
	Study/Ttrial Completion:	February 2012
	Final Report Submission:	October 2012
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The applicant did not provided information on the potential effects of the drug on late stage of pregnancy, neonatal development and the effect of the drug on reproductive performance of second generation as requied according to the ICH guidelines.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Results of the study would provide non-clinical data on the delivery, weaning and reproductive performance of the second generation in a non-clinical species. Currently, the product is approved with a labeling statement that no data are available and caution to the nursing women. Therefore, the non-clinical data would provide assessment of potential risk and appropriate monitoring of patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The recommended study is a non-clinical study where pregnant female rats will be treated during the last stage of pregnancy through the nursing period and the mature second generation rats would be assessed for their reproductive performance.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Conduct an 18-month study in dogs to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	May 2011
	Study/Ttrial Completion:	November 2012
	Final Report Submission:	July 2013
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The applicant needs to evaluate the potential long-term consequences to vacuole formation in several organs including adrenal glands and aortic outflow with histopathological assessment and its reversibility in dogs. The information would be used for the long term monitoring of patients if an untoward effect is observed in these organs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Results of the study would provide non-clinical data on the safety of adrenal glands and cardiovascular systems due to a chronic treatment with KRYSTEXXA. A 6-month study was conducted in dogs that met the ICH guideline and criteria for the assessment of chronic non-clinical safety. However, the review team recommended a longer exposure and reversibility of the lesions so that appropriate precautions could be given to patients. The target organs of toxicity and its effects could not be clearly determined with reversibility of the lesions in the 6-month toxicity study in dogs.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Chronic treatment of dogs for 12 months followed by a 6-month recovery.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To redevelop the anti-PEG antibody assay to address the issues of high degree of intra-and-inter-assay variability observed in the current ELISA

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	MM/DD/YYYY
Study/Clinical trial Completion Date:	MM/DD/YYYY
Final Report Submission Date:	April 2011
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The current anti-PEG antibody ELISA is acceptable but could be optimized further in order to provide better safety monitoring. Over 80% of the patients develop antibodies to pegloticase, and the majority of the antibodies appear to be directed against the PEG portion rather than the uricase therapeutic enzyme. Given there is a new safety study being performed, it would be useful to have an optimized assay in order to monitor anti-PEG antibody levels more accurrately

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current anti-PEG antibody ELISA shows a very high degree of intra-and inter-assay variability possibly related to the PEG coating of the ELISA plate. This indicates either that the assay is not sufficiently optimized or that the format is unsuitable. Sponsor is requested to redevelop the anti-PEG antibody ELISA to address the above concerns.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of samples obtained in new safety study.Sponsor is requested to provide data to assess the immunogencity of the product and its potential clinical impact using the re-developed assay. Patients that become positive for anti-PEG antibody should have their antibody levels tracked until they revert to sero-negative status.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☒ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other
  Immunogenicity study as a marker of safety

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

   - ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   - ☒ Are the objectives clear from the description of the PMR/PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To redevelop the anti-IgE antibody assay to increase sensitivity of current assay (ELISA) to detect IgE antibodies to Pegloticase. Consider using ECL technology.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	MM/DD/YYYY
Study/Clinical trial Completion Date:	MM/DD/YYYY
Final Report Submission Date:	October 2012
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The sensitivity of IgE assay, as currently designed, is insufficient to detect IgE antibodies to the product. According to the review by Dr. Susan Limb approximately 5% of patients had reactions the Agency considers anaphylactic. Since there is no medical alternative to this treatment for some patients understanding whether the anaphylactic reactions are IgE mediated might impact future treatment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sensitivity of your IgE assay, as currently designed, is insufficient to detect IgE antibodies to the product. For an antigen specific IgE assay to be useful, it should have sensitivity in the nanogram to sub-nanogram range, and there are technologies currently available that can meet this criterion. Develop a more sensitive antigen specific IgE ELISA assay. Consider using ECL technology. Your IgE assay was not properly validated due to a lack of positive control antibody. Develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of samples obtained in new safety study.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Immunogenicity study as a marker of safety

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

SMS 9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Develop a suitable positive control for the Pegloticase specific IgE ELISA.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	MM/DD/YYYY
Study/Clinical trial Completion Date:	MM/DD/YYYY
Final Report Submission Date:	January 2012
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☒ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

The IgE assay was not properly validated due to a lack of positive control antibody. Sponsor needs to develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option. According to the review by Dr. Susan Limb approximately 5% of patients had reactions the Agency considers anaphylactic. Since there is no medical alternative to this treatment for some patients understanding whether the anaphylactic reactions are IgE mediated might impact future treatment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Your IgE assay was not properly validated due to a lack of positive control antibody. Develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of samples obtained in new safety study.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☒ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☒ Other
  Immunogenicity study as a marker of safety

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

   - ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   - ☒ Are the objectives clear from the description of the PMR/PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

SM 9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. Submit the new acceptance criteria for the assay.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Ttrial Completion:	MM/DD/YYYY
Final Report Submission:	September 2012
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor needs additional time to manufacture 20 to 50 Krystexxa lots to establish accurate acceptance criteria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Drug product release acceptance criteria are established based on clinical experience, manufacturing historic trends and capability. The sponsor has only manufactured three drug product lots using the validated process to support approval of this BLA. The sponsor needs to manufacture additional lots of Krystexxa to establish accurate acceptance criteria for the peptides detected in the Krystexxa lysine site occupancy assay.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over and under pegylated uricase molecules. Submit the results of the study.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Ttrial Completion:	MM/DD/YYYY
Final Report Submission:	January 2011
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

The validation studies for drug product release assay to measure lysine site occupancy with mPEG on Krystexxa are adequate at this time to recommend approval of the application.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor has developed and implemented a scientifically validated peptide map assay to monitor the peg distribution on the uricase molecule for release of the Krystexxa drug product. However, data have not been provided in this CR submission to evaluate the sensitivity of the assay to detect potential changes in the distribution of peg on the uricase molecule. The sensitivity of the assay can be evaluated by analyzing pegylated uricase that has been intentionally over or under pegylated. This study can be done using pegylated uricase manufactured at the laboratory scale.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To re-evaluate the release and stability acceptance criteria for the following assays;

a. enzymatic activity
b. Km and kcat determination by product accumulation and substrate depletion
c. monomer and HMW forms by SEC-HPLC Abs220
d. monomer HMW and LMW forms by Abs220

The acceptance criteria for the drug substance and drug product will be reevaluated and after 30 lots are manufactured. Submit the revised specifications for release acceptance criteria.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Ttrial Completion:	MM/DD/YYYY
Final Report Submission:	September 2012
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor needs additional time to manufacture 20 to 50 Krystexxa lots to establish accurate acceptance criteria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Drug substance and product release acceptance criteria are established based on clinical experience, manufacturing capability and history. The sponsor has only manufactured three drug substance and product lots using the validated process to support approval of this BLA. The sponsor needs to manufacture additional lots of Krystexxa to establish accurate acceptance criteria for the potency and product related impurity assays.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To re-evaluate the release and stability acceptance criteria for the following assays;

a. enzymatic activity
b. Km and kcat determination by product accumulation and substrate depletion
c. monomer and HMW forms by SEC-HPLC Abs220
d. monomer HMW and LMW forms by Abs220

The acceptance criteria for the drug substance and drug product will be reevaluated and after 30 lots are manufactured. Submit the revised specifications for stability acceptance criteria.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Ttrial Completion:	MM/DD/YYYY
Final Report Submission:	June 2013
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor needs additional time to manufacture 20 to 50 Krystexxa lots to establish accurate acceptance criteria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Drug substance and product release acceptance criteria are established based on clinical experience, manufacturing capability and history. The sponsor has only manufactured three drug substance and product lots using the validated process to support approval of this BLA. The sponsor needs to manufacture additional lots of Krystexxa to establish accurate acceptance criteria for the potency and product related impurity assays.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To develop and implement an enzymatic assay, based on a measure of product accumulation, that determines Km and kcat values for release of uricase intermediate. Submit the new specification and supporting data.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Ttrial Completion:	MM/DD/YYYY
	Final Report Submission:	December 2012
	Other: Validation Report Completion	June 2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor needs additional time to develop and implement a superior Km and kcat kinetic parameter potency assay for release of the uricase intermediate. The substrate depletion assay, currently used for release testing, is sufficient to support approval of the BLA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor has implemented an assay based on substrate depletion for the Km and kcat kinetic parameters for this potency assay. In general substrate depletion assays are suboptimal since they tend to be less accurate than product accumulation assays. The sponsor has developed and implemented a product accumulation assay for release of the drug substance and drug product. The sponsor has not been able to develop a similar assay for the uricase intermediate since the Km for the molecule is very low and the assay precision is poor. It is impractical to establish the assay for release of the uricase intermediate at this time. The sponsor therefore needs additional time to develop and implement the assay for release of the uricase intermediate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Sue 9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To include stress conditions in the annual stability program for drug substance and drug product. Submit the revised stability protocols.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Ttrial Completion:	MM/DD/YYYY
Final Report Submission:	January 2011
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The current stability protocol is sub optimal, but sufficient to recomment approval of the BLA at this time.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current post-marketing stability commitment only provides for stability data acquired at the proposed storage temperature. However, the purpose of the annual stability program is not solely to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Performing stability studies under stress conditions models such effects.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Evaluate in-use stability of the drug product by assessing the impact of dilution of 1.0 mL drug product (pH 7.0) into 250mL saline solution under the worst case scenario pH (pH 4.5), and determine the final pH of the infusion solution. Submit the results of the study and risk mitigation strategies, if the final pH is below 6.2.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Ttrial Completion:	April 2011
	Final Report Submission:	July 2011
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The dilution for administration stability studies provided in the BLA are suboptimal. They do not address the worst case scenario in which Krystexxa is dilute into USP saline for injection with a pH of 4.5. They are however adequate at this time since product was diluted into commercial saline and maintained a pH of 6.2 -7.0 and the product remained stable. The information provided in the BLA is sufficient to recommend approval of the application at this time since there is a very low risk that product will not remain stable after dilution into USP saline.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Krystexxa is administered in 0.45% or 0.90% USP sodium chloride. The USP pH specification for the saline is 4.5 to 7.0. 1 ml of Krystexxa is dilute into 250 ml of saline. Krystexxa is formulated in PBS (pH 7.0 - 7.6). Given the wide pH acceptance criteria of USP saline for injection, there was some concern that the product may be exposed to wide pH ranges after dilution into saline. In the BLA, the sponsor has provided a study report in which the product is diluted into different lots of saline (B Braun Midical and Hospira infusion bags) and pH was analyzed. The pH ranged from 6.2 to 7.0 after dilution and the product remained stable over the 72 hr time period. The study did not provide for the worst case condition in which Krystexxa is diluted in to saline with a pH of 4.5. The sponsor should evaluate the product when it is diluted under these conditions to make sure that the product remains stable over the proposed four hour time period.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

9/14/10

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Provide the results of aseptic fill validation and results of stability studies on three batches of KRYSTEXXA held for at least six months to support the reduction of the drug product vial overfill to that recommended in the USP.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	November 2010
	Study/Ttrial Completion:	March 2011
	Final Report Submission:	January 2012
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor should justify the use of a (b) (4) for delivery of 1.0 ml to be compliant with FDA regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor fill (b) (4) of Krystexxa for delivery of 1.0 ml. 21 CFR 201.51(g) states that "the minimum quantity above the stated measure shall comply with the excess volume prescribed by the National Formulary or the USP". The USP Injection monograph specifies that for a 1.0 ml label the recommended excess volume cannot exceed 1.10 ml. The sponsor is therefore currently overfilling the vial by (b) (4) The sponsor must justify this overfill or decrease the fill volume to be compliant with US regulations. Acceptable justification would include that a 1.10 ml fill volume is not adequate to deliver 1.0 ml to the patient due to los of the product in the vial and syringe during preparation of Krystexxa in the pharmacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

NA

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

SMS 9/14/10

(signature line for BLAs)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality
International Compliance Team, HFD-325
10903 New Hampshire Avenue – WO51
Silver Spring, MD 20993

TELEPHONE: (301) 796-3251
FAX: (301) 827-8908

July 28, 2009

To: Diana Walker, Ph.D., Regulatory Health Project Manager,
Office of Drug Evaluation II, Division of Anesthesia, Analgesia, and Rheumatology Products

From: Colleen Hoyt, Compliance Officer, Manufacturing Assessment and Preapproval Compliance Branch, Division of Manufacturing and Product Quality, CDER Office of Compliance

Thru: Concepcion Cruz, Acting Branch Chief, Manufacturing Assessment and Preapproval Compliance Branch, Division of Manufacturing and Product Quality, CDER Office of Compliance

Subj: Recommendation to Withhold Approval
Pegloticase, STN 125293/0
Savient Pharmaceuticals, Inc. aka Bio-Technologies General, Corp.
FEI: 3000164186

The Manufacturing Assessment and Preapproval Compliance Branch has completed the review and evaluation of the establishment evaluation request for STN 125293/0, Savient Pharmaceuticals, Inc., East Hanover, NJ, Krystexxa™ (pegloticase). Based on the significance of the deficiencies found during the 6/3-10/09 preapproval inspection of the contract bulk drug substance manufacturer, Bio-Technologies General Corporation, located in Kiryat Malachi, Be-er Tuvia, Israel, CDER Office of Compliance is currently pursuing regulatory action and cannot recommend approval of STN 125293/0 at this time.

Should you have any questions regarding the status of this case, please contact Maan Abduldayem, Compliance Officer, International Compliance Branch at 301-796-3916.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 23, 2009

TO: Diana Walker, Ph.D., Regulatory Project Manager
Rosemarie Neuner, M.D., M.P.H., Medical Officer
Jeffrey Siegel, M.D., Medical Team Leader
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: #125293

APPLICANT: Savient Pharmaceuticals

DRUG: Krystexxa (pegloticase)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: control of hyperuricemia and management of the signs and symptoms of gout.

CONSULTATION REQUEST DATE: December 18, 2008

DIVISION ACTION GOAL DATE: June 30, 2009
PDUFA DATE: July 30, 2009

I. BACKGROUND

BLA 125293 is an original BLA for a new molecular entity, pegloticase (PEG-uricase), a genetically engineered recombinant porcine uricase (urate oxidase), for the indication of control of hyperuricemia and management of the signs and symptoms of gout. Inspections of clinical sites were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. Clinical sites were chosen for the large number of enrolled subjects and for the occurrence of adverse events. Inspection of the sponsor was conducted because this is a new molecular entity. Inspection of the clinical laboratory, Charles River Laboratories Preclinical Services, was conducted because the clinical sites were blinded to the primary endpoint, plasma uric acid concentrations.

The protocols inspected were Protocols: #CO405 and #CO406, two identical studies entitled "Randomized, multicenter, double-blind, placebo-controlled efficacy and safety study of 8mg PEG-uricase in two dose regimens in hyperuricemia subjects with symptomatic gout."

II. RESULTS (by Site):

Name of Clinical Investigator (CI), Clinical Laboratory (CL), or Sponsor, and Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI #1 Stephen Bookbinder, MD 3210 SW 33rd Road Suite 102 Ocala, FL 34474	C0405/ 8 subjects	May 11 to 15, 2009	VAI
CI #2 John S. Sundy, MD, PhD Duke University Medical Center 014 Baker House Box 3278 Durham, NC 27710	C0405/ 11 subjects	February 10 to 13, 2009	NAI
CI #3 Herbert S.B. Baraf, MD The Center for Rheumatology and Bone Research 2730 University Boulevard, West Suite 306 Wheaton, MD 20902	C0406/ 13 subjects	February 4 to 5, 2009	NAI
Sponsor Savient Pharmaceuticals, Inc One Tower Center, 14th Floor East Brunswick, NJ 08816	C0405 and C0406	February 26 to March 6, 2009	NAI
CL Charles River Laboratories Preclinical Services Montreal 22022, Transcanadienne Senneville Quebec, H9X 3R3 Canada	C0405 and C0406	March 23 and 24, 2009	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. Stephen Bookbinder, MD
   3210 SW 33rd Road, Suite 102
   Ocala, FL 34474

   a. **What was inspected**: For protocol #CO405, 12 subjects were screened, 8 subjects were randomized, and 5 subjects completed the study. An audit of all subjects' records was conducted. There were no limitations to the inspection.

b. **General observations/commentary:** One subject died of complications of a pre-existing conditions (congestive heart failure and renal failure). One subject withdrew consent after experiencing a post-infusion reaction, and one subject was terminated by the clinical investigator due to exacerbation of a pre-existing migraine condition. There was one adverse event of dry skin (moderate) in subject 102010 that was listed in the adverse event log on May 2 to May 19, 2007 but was not reported to the sponsor.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. John S. Sundy, MD, PhD
Duke University Medical Center, 014 Baker House
Box 3278, Durham, NC 27710

a. **What was inspected:** For protocol #CO405, 12 subjects were screened, 11 subjects were randomized, and 10 subjects completed the study. An audit of all subjects' records was conducted. There were no limitations to the inspection.

b. **General observations/commentary:** There was no under-reporting of adverse events and no regulatory violations noted.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Herbert S.B. Baraf, MD
The Center for Rheumatology and Bone Research
2730 University Boulevard, West, Suite 306
Wheaton, MD 20902

a. **What was inspected:** For protocol #CO406, 17 subjects were screened, 13 subjects were randomized, and 8 subjects completed the study. An audit of all subjects' records was conducted. There were no limitations to the inspection.

b. **General observations/commentary:** There was no under-reporting of adverse events and no regulatory violations noted.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Savient Pharmaceuticals, Inc
One Tower Center, 14th Floor
East Brunswick, NJ 08816

a. **What was inspected**: The inspection reviewed the following sponsor responsibilities: contract research organizations, monitoring plans, test article accountability, financial disclosures, qualifications of investigators and site monitors, transfer of obligations, and adverse event (AE) reports.

b. **General observations/commentary**: The sites appeared to be adequately monitored during the two studies. It was noted that AEs were addressed and reported according to the site visit reports created by the monitors. There were no regulatory violations noted.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Charles River Laboratories Preclinical Services
Montreal 22022, Transcanadienne Senneville
Quebec, H9X 3R3 Canada

a. **What was inspected**: To verify the endpoint data, the inspection reviewed all plasma uric acid levels available at time points at three and six months for all 32 subjects identified at the clinical sites. Data provided by Charles River Laboratories was compared with the data submitted by Savient Pharmaceuticals, Inc. to the BLA. According to the laboratory work plan, a correction factor of .87 (13%) was applied to all the values provided by Charles River Laboratories.

b. **General observations/commentary:** There were no discrepancies of the collection dates, subject numbers and uric acid values between the laboratory source data and the data submitted in the BLA.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of all clinical sites, the sponsor, and the contract laboratory did not note any regulatory violations.

The studies appear to have been conducted adequately, and the data generated by the clinical sites and the laboratory may be used in support of the respective indication.

Susan Leibenhaut, MD
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, MD, MPH
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: July 20, 2009

To: Diana Walker – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
BLA 125293 KRYSTEXXA™ (pegloticase) Injection, for intravenous infusion

---

DDMAC has reviewed the proposed revised product labeling (PI) for KRYSTEXXA™ (pegloticase) Injection, for intravenous infusion (Krystexxa) submitted for review on July 20, 2009.

Thank you for the opportunity to comment on this revised label. If you have any questions about DDMAC's comments, please do not hesitate to contact Mathilda Fienkeng at (301) 796 3692 or mathilda.fienkeng@fda.hhs.gov.

17 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

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:	May 15, 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 7/1/09 Denise Toyer, Pharm.D., Deputy Director D.P. Toyer 6/30/09 Carol Holquist, R.Ph., Director C Holquist 7/1/09 Division of Medication Error Prevention and Analysis
From:	Cathy A. Miller, M..P.H., Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Krystexxa (Pegloticase) for Intravenous Infusion 8 mg Uricase Protein/mL
Application Type/Number:	BLA 125293
Applicant:	Savient Pharmaceuticals, Inc.
OSE RCM #:	2008-1799

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

CONTENTS

EXECUTIVE SUMMARY

The container labels and carton labeling for Krystexxa were provided as part of a request for the evaluation of a proprietary name review on November 14, 2008. Our review of the proposed labels and labeling noted the Applicant's use of certain language and abbreviations in the package insert labeling that may lead to confusion during dosage and administration. Additionally information is lacking on container labels and carton labeling that would help to prevent the inappropriate preparation of the product.

The deficiencies we have identified can be addressed and mitigated prior to approval. We have provided recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 REGULATORY HISTORY

In conjunction with this submission, the Applicant also submitted a request for review of the proposed proprietary name, Krystexxa, which was reviewed separately by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable in OSE Review #2008-1886 dated January 5, 2009.

1.2 PRODUCT INFORMATION

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. Pegloticase is given intravenously every two weeks (b) (4)

Pegloticase is available as a 1 milliliter (mL) sterile solution for dilution in a single-use 2 mL glass vial, containing 8 mg of Uricase Protein/mL for intravenous infusion. Pegloticase 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. Pegloticase should be only administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. Pegloticase should not be administered as an intravenous push or bolus. (b) (4) it is recommended that diluted solutions be stored under refrigeration. Admixed solutions of Pegloticase 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 the methods and materials used by the Division of Medication Error Prevention and Analysis' conducting a label, labeling, and/or packaging risk. 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 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 package 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.[2]

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

For this product, the review division forwarded the following label and labeling for our review. (See Appendices A through D):

- Container Label for 2 mL Vial
- Outer Carton Labeling
- Fold-Out Carton Labeling
- Carton Labeling Peel-Off Sticker

3 RESULTS

Review of the container labels and carton labeling for Pegloticase has identified the following areas of vulnerability that could lead to medication error.

---

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

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

3.1 PRESENTATION OF THE DOSAGE FORM

3.1.1 The dosage form following the established name is presented as "For IV Infusion" which includes the abbreviation 'IV' rather than the full spelling of 'Intravenous' on all container labels and carton labeling.

3.1.2 The dosage form throughout product labeling uses the word 'Infusion' (For Intravenous Infusion) rather than the conventional presentation (For Intravenous Injection) seen in drug products that are diluted or reconstituted and given intravenously.

3.1.3 The presentation of the dosage form in the Highlights of Prescribing Information of the Package Insert labeling includes the word (b) (4) .

3.2 NORMAL SALINE AND HALF NORMAL SALINE PRESENTATION IN INSERT LABELING

Section 2.2 Preparation includes (b) (4) (b) (4) included with the correct U.S. Pharmacopeia presentations '0.9 % Sodium Chloride Injection, USP' and 0.45 % Sodium Chloride Injection, USP'.

3.3 DILUTE BEFORE ADMINISTRATION STATEMENT

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. Additionally, the dilution statement does not appear on the principal display panel of the fold-out out carton labeling or the container label.

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information on the container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors.

4.1 PRESENTATION OF THE DOSAGE FORM ON CONTAINER LABELS AND CARTON LABELING

The dosage form following the established name on container labels and carton labeling includes the abbreviation 'IV" rather than spelling out the word 'Intravenous'. In June 2006, the Institute for Safe Medication Practices (ISMP) and the Food and Drug Administration launched a national education campaign to eliminate preventable sources of medication errors that occur from the use of ambiguous medical abbreviations. Post-marketing experience has shown that medication errors have occurred due to the misinterpretation of abbreviations used in prescribing practices. While consulting with the Office of Biotechnology Products (OBP), they also concurred that 'IV' should be spelled out as 'Intravenous' in labels and labeling for Pegloticase.

Additionally, we note that the Applicant presents the dosage form as [redacted] We consulted with OBP to obtain clarity on the use of the word [redacted] in the Applicant's presentation of the dosage form as we found its use unacceptable. OBP concurs with our assessment that the word [redacted] should not be included in the presentation of the dosage form in package insert labeling.

Lastly, we note that the Applicant's uses an unconventional presentation of the dosage form 'For Intravenous Infusion' throughout labeling. The dosage form for CDER drug products administered intravenously after dilution or reconstitution is presented as "For Intravenous Injection". However, we defer further evaluation of this issue to the FDA Labeling and Nomenclature Committee.

4.2 DILUTE BEFORE ADMINISTRATION STATEMENT ON CONTAINER LABELS AND CARTON LABELING

CDER drug products that require dilution prior to administration are presented typically contain the statement "Must be Diluted Prior to Administration". DMEPA consulted with DAARP Review Team on the Application's selected language "Dilute Before Administration" and they concur 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 fold-out carton labeling which holds the 1 mL vial of Pegloticase and the container labels do not contain the "Dilute Before Administration" statement that appears on the principal display panel of outer carton labeling. DMEPA understands that the limited space availability on the 1 milliliter vial container label may make it difficult to add such language however, we recommend the statement's inclusion on the fold-out carton labeling. Because Krystexxa requires dilution before administration, the "Dilute Before Administration" statement may help to minimize the risk of maladministration of the drug.

4.2.1 Normal Saline and Half Normal Saline Presentation in Insert Labeling

Including [redacted]' along with '0.9% Sodium Chloride Injection, USP' and '0.45 % Sodium Chloride Injection, USP' is redundant.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels, carton labeling and insert labeling introduce vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis has identified areas of needed improvement in container labels, and carton labeling. We have provided the following recommendations in Section 5.2

and request this information be forwarded to the Applicant. We have discussed recommendations one through three with OBP and they concur with DMEPA.

Additionally, we identified that the Applicant's presentation of the dosage form throughout labeling is "For Intravenous Infusion". The dosage form for drug products that are for intravenous administration after dilution or reconstitution within CDER are presented as "For Intravenous Injection". We request that the FDA Labeling and Nomenclature Committee evaluate this issue and therefore, defer to their recommendations.

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

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the container labels, carton labeling and insert labeling, and have identified areas of needed improvement. We request you revise the following:

A. Container Label (8 mg/mL)

1. Revise the presentation of the dosage form to spell out the word IV so it reads Intravenous.
2. Add the dilution statement to the principal display panel of the container label, if space permits.

B. Carton Labeling (1 x 8 mg/mL vial)

1. Revise the presentation of the dosage form to spell out the word IV so it reads Intravenous.
2. Revise the dilution statement that appears on carton labeling to read "Must Be Diluted Prior to Administration" rather then the current presentation "Dilute Before Administration".
3. Add the dilution statement to the principal display panel of the fold-out carton labeling.

C. Insert Labeling

1. Remove the word [redacted (b) (4)] from the presentation of the dosage form where it appears in the Highlights of Prescribing Information section of the package insert labeling.
2. Remove the words [redacted (b) (4)] and [redacted (b) (4)] from Section 2.2 Preparation, paragraph two in the Package Insert Labeling, as this information is redundant since it is also listed as "0.45 % Sodium Chloride Injection, USP and 0.9 % Sodium Chloride Injection, USP".

2 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: March 11, 2009

To: Diana L. Walker, PhD – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Samuel M. Skariah, Pharm.D. – Regulatory Review Officer
Michael Sauers – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Sangeeta Vaswani, Pharm.D. – Group Leader
Robert Dean, MBA – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
BLA #125293 KRYSTEXXA™ (pegloticase) Concentrated solution for intravenous infusion

---

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, and proposed carton and container labeling for KRYSTEXXA™ (pegloticase) (b) (4) solution for intravenous infusion (Krystexxa) submitted for consult on November 12, 2008.

The following comments are provided using the updated version of the proposed PI and Medication Guide, dated February 4, 2009. DDMAC's comments are provided directly in the attached document.

DDMAC does not have any comments regarding the proposed carton and container labeling for Krystexxa.

Thank you for the opportunity to comment on this label. If you have any questions, please contact Sam Skariah at 301.796.2774 or Michael Sauers at 301.796.1035.

23 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/ TS)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: BLA 125293

Name of Drug: Pegloticase for IV infusion, 8 mg uricase protein/mL

Applicant: Savient Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): October 31, 2008

Receipt Date(s): October 31, 2008

Submission Date of Structure Product Labeling (SPL): October 31, 2008

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

HIGHLIGHTS:

- The reference for [redacted] (b) (4) (5.4), must be added.
- Do not use the ® symbol in Highlights.
- The Tradename must appear in bold type.
- Remove the empty line before the Initial US Approval statement.
- Include criteria for determining Adverse Reactions (e.g., incidence rate greater than x%).
- The Revision Date must appear in bold type.

FULL PRESCRIBING INFORMATION: CONTENTS:

- A horizontal line must be located between the Table of Contents and the Full Prescribing Information Section.
- Remove periods after section numbers for 7, 8, 10, 11, and 12.
- Section Headings 7 though 17 should be in bold.
- Remove Section Heading 9, as there is no Drug Abuse and Dependence section in the Full Prescribing Information Section.
- In Section 8, subsections must retain their designated numbers. If subsection 8.2 is skipped, 8.2 should be omitted. Continue Nursing Mothers as subsection 8.3, etc. Patients with Renal Impairment will be designated subsection 8.6.

FULL PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS:

- Remove the extra line (line 161).

USE IN SPECIFIC POPULATIONS:

- Re-number the subsections to correctly correspond to the Table of Contents, as describes above.
- A Pregnancy Category (A, B, C, D or X) will be inserted by the FDA Review team.

PATIENT COUNSELING INFORMATION:

- Remove line 672, "Last Modified: 10/15/2008".

Diana L. Walker, PhD
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

Drafted: DWalker/27Jan09
Revised/Initialed: 03Feb09
Finalized: 03Feb09
CSO LABELING REVIEW OF PLR FORMAT

DEC 2 9 2008

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125293/0	NDA Supplement #:S- BLA STN # 125293	Efficacy Supplement Type SE-
Proprietary Name: Krystexxa™ (proposed) Established/Proper Name: Pegloticase, also known as PEG-uricase and PURICASE® Dosage Form: Parenteral Strengths: 8 mg uricase protein/mL		
Applicant: Savient Pharmaceuticals, Inc. Agent for Applicant (if applicable): Murad Husain, VP Regulatory Affairs		
Date of Application: October 31, 2008 Date of Receipt: October 31, 2008 Date clock started after UN:		
PDUFA Goal Date: April 30, 2009	Action Goal Date (if different): April 30, 2009	
Filing Date: December 30, 2008 Date of Filing Meeting: December 15, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Pegloticase is a bio-uricolytic agent indicated for treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout.		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☐ Standard ☒ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 10,122	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:** Orphan designation	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☐ YES ☒ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☒ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**: BLA, no patent information included.	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**: Reviewer's Guide	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☒ Not Applicable ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Note: *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: **Orphan designation-PREA not required**	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☐ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): July 26, 2005 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): April 17, 2008 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**: Protocol C0405	☒ YES Date(s): May 3, 2006 ☐ NO

ATTACHMENT

DEC 2 9 2008

Diana Walker

MEMO OF FILING MEETING

DATE: December 15, 2008

BLA #: 125293/0

PROPRIETARY/ESTABLISHED NAMES: Pegloticase

APPLICANT: Savient Pharmaceutical, Inc.

BACKGROUND: This submission is a new original BLA for Pegloticase, (also known as PEG-uricase and Puricase) for intravenous infusion intended for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout. This product has received Orphan Drug Designation and will be under Priority review (6 month clock).

REVIEW TEAM:

Discipline/Organization	**Names**		**Present at filing meeting? (Y or N)**
Regulatory Project Management	RPM:	Diana L. Walker	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Jeffrey Siegel		Y
Clinical	Reviewer:	Rosemary Neuner	Y
	TL:	Jeffrey Siegel	Y
Social Scientist Review (*for OTC products*)	Reviewer:		N/A
	TL:		N/A
Labeling Review (*for OTC products*)	Reviewer:		N/A
	TL:		N/A
OSE	Reviewer:	Kathryn O'Connell OSE/DRISK	Y
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		N/A
	TL:		N/A

Clinical Pharmacology	Reviewer:	Ping Ji Atul Bhattaram	Y Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Ruthanna Davi	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Belinda Hayes	Y
	TL:	Daniel Mellon (Adam Wasserman-for Dan Mellon)	N Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Howard Anderson Richard Ledwidge	Y Y
	TL:	Emanuela Lacana	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	Mary Farbman	Y
	TL:	Patricia Hughes	Y
Microbiology (Facilities)	Reviewer:	Bo Chi	Y
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Constance Lewin	Y
Other reviewers: Immunogenicity	Joao Pedras-Vasconcelos (Reviewer) Daniela Verthely (Reviewer) Susan Kirschner (Team Leader)		Y Y Y

OTHER ATTENDEES:
Chris Wheeler, RPM, OSE
Leah Ripper, RPM, ODEII
Rigoberto Roca, Deputy Director, DAARP
Bob A. Rappaport, Director, DAARP

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain:	

Electronic Submission comments **List comments**: Some tables in the submission were unreadable.	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter (to be sent at 60 days)
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: March 5, 2009 ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA**	☒ YES ☐ NO ☐ YES ☐ NO

supplements only)	
FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curt Rosebraugh

GRMP Timeline Milestones: **60 day date = December 30, 2008**
MidCycle = January 27, 2009
AC Meeting = March 5, 2009
WrapUp = March 24, 2009
Labeling and PMR Communication = March 26, 2009
Action Date = April 30, 2009

Comments:

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Cardiovascular Signal ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If BLA or Priority Review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74 – sent by day 60
☐	Other

SEALD LABELING REVIEW

APPLICATION NUMBER	BLA 125293
APPLICANT	Savient Pharmaceuticals, Inc.
DRUG NAME	PEGLOTICASE
SUBMISSION DATE	October 31, 2008
SEALD REVIEW DATE	July 2, 2009
SEALD REVIEWER(S)	Abiola Olagundoye, PharmD 7/7/09 7/7/09
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

21 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/ TS)