

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203389Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # NDA 203389	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: PROCYSBI Established/Proper Name: cysteamine bitartrate delayed release Dosage Form: capsules Strengths: 25mg, 75mg		
Applicant: Raptor Therapeutics		
Date of Receipt: 3/30/2012		
PDUFA Goal Date: 4/30/2013	Action Goal Date (if different):	
RPM: Jessica Benjamin		
Proposed Indication(s): treatment of nephropathic cystinosis		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20392 for Cystagon	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant bridged the proposed product to the reference product through assessments of assay and impurity profiles and pharmacokinetic/pharmacodynamic studies performed in patients with nephropathic cystinosis and bioequivalence studies in healthy volunteers.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Cystagon	NDA 20392	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosing frequency (every 6 hours for Cystagon [the reference product] compared to every 12 hours for Procysbi [the proposed drug product]. Cystagon is an immediate release, while Procysbi is a delayed-release.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A" If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If **“YES”** *and* there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** *or* if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 200740 [CYSTARAN (cysteamine ophthalmic solution) 0.44%]

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN
04/26/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	PROCYSBI (cysteamine bitartrate) delayed-release capsules, for oral use
Applicant	Raptor Pharmaceuticals, Corp.
Application/Supplement Number	NDA 203389
Type of Application	Original Submission
Indication(s)	For the management of nephropathic cystinosis in adults and children ages 6 years and older
Established Pharmacologic Class ¹	cystine depleting agent
Office/Division	ODE III/DGIEP
Division Project Manager	Jessica Benjamin
Date FDA Received Application	March 30, 2012
Goal Date	April 30, 2013
Date PI Received by SEALD	April 26, 2013
SEALD Review Date	April 26, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL is >1/2 page. DGIEP notified and provided suggestions to reduce HL to 1/2 page. Will reduce HL if possible, or will have to grant waiver.*

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Use in Specific Populations heading is not in the center of a complete horizontal line.*

- NO** 4. White space must be present before each major heading in HL.

Comment: *White space is missing before the Dosage and Administration and Adverse Reactions headings in HL. (There is too much white space before the Use in Specific Populations heading.)*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Under the Dosage and Administration heading in HL, the reference is missing for: the first three bulleted items; the 6th and 7th bulleted items; and, the last statement "See Full Prescribing Information for details on administration."*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Selected Requirements of Prescribing Information

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: Subsection 2.7 use lower case letter for the word "from"; subsection 4.1, use title case letter for the word "Penicillamine"; subsection 6.2, there should be no "dash" between the word "Postmarketing".

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: The numbering for subsection 17.3 appears "twice" in the FPI. Delete one of the "17.3" numbers.

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: The FDA-approved patient labeling (Patient Information) does not appear at the end of the PI.

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: Do not use headings within a subsection in the format of the cross reference. Use the format described above. Correct the mistakes in subsections 12.2 "(See Section 2.6 Dose Titration)" and subsection 14.1 "[See Dose Titration (2.6)]". The correct cross reference for both is [See Dosage and Administration (2.6)]. Also, in subsection 14.2, the cross reference should read [See Nonclinical Toxicology (13.1)], not (13).

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Selected Requirements of Prescribing Information

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
04/26/2013

LAURIE B BURKE
04/29/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: April 26, 2013

To: Jessica Benjamin, Senior Regulatory Project Manager
Division of Gastrointestinal and Inborn Error Products
(DGIEP)

From: Matthew Falter, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Acting Group Leader, OPDP

Subject: NDA # 203389
OPDP Labeling Comments for PROCYSBI (cysteamine
bitartrate) delayed-release capsules, for oral use (Procysbi)

OPDP has reviewed the proposed Package Insert (PI), Patient Package Insert (PPI) and Carton and Container Labeling for Procysbi submitted for consult on June 7, 2012.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "procysbi label.doc" that was sent via email from DGIEP to OPDP on April 12, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP's comments on the PPI are based on the draft marked-up PPI titled "cysteamine bitartrate (PROCYSBI) N 203389 DMPP PPI 4-2013 clean(1).doc" that was sent via email from the Division of Medical Policy Programs to DGIEP and OPDP on April 26, 2013. We have no comments on the proposed PPI at this time.

OPDP has reviewed the proposed carton and container labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\EVSPROD\NDA203389\0029\m1\us\114-label\1141-draft-label\contain-25mg-capsule.pdf>

- <\\cdsesub1\EVSPROD\NDA203389\0029\m1\us\114-label\1141-draft-label\contain-75mg-capsule.pdf>

We have no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding this review, please contact Matthew Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW J FALTER
04/26/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: April 26, 2013

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Error Products
(DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): PROCYSBI (cysteamine bitartrate)

Dosage Form and Route: delayed-release capsules, for oral use

Application Type/Number: NDA 203-389

Applicant: Raptor Pharmaceuticals Corporation

1 INTRODUCTION

On March 30, 2012, Raptor Pharmaceuticals Corporation submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 203-389 PROCYSBI (cysteamine bitartrate) delayed-release capsules. The Reference Listed Drug for this application is CYSTAGON, NDA 20-392. The proposed indication for PROCYSBI (cysteamine bitartrate) delayed-release capsules is for the management of nephropathic cystinosis in adults and children 6 years of age and older. On March 28, 2013, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for PROCYSBI (cysteamine bitartrate). The Applicant originally submitted a Medication Guide (MG) with this NDA; however, DGIEP subsequently notified the Applicant that a MG is not required for this product and that it would be converted to a PPI.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for PROCYSBI (cysteamine bitartrate) delayed-release capsules.

2 MATERIAL REVIEWED

- Draft PROCYSBI (cysteamine bitartrate) delayed-release capsules Medication Guide (MG) received on March 30, 2012, converted to a Patient Package Insert (PPI) and revised by the Review Division throughout the review cycle, and retrieved from DGIEP eRoom by DMPP on April 16, 2013.
- Draft PROCYSBI (cysteamine bitartrate) delayed-release capsules Prescribing Information (PI) received on March 30, 2012, revised by the Review Division throughout the review cycle, and retrieved from the DGIEP eRoom by DMPP on April 17, 2013.
- Approved CYSTAGON (cysteamine bitartrate) Capsules comparator labeling dated June 6, 2007.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

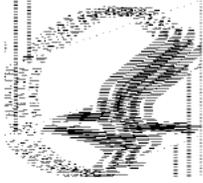
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/s/

SHARON R MILLS
04/26/2013

BARBARA A FULLER
04/26/2013

LASHAWN M GRIFFITHS
04/26/2013



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**PEDIATRIC AND MATERNAL HEALTH STAFF,
MATERNAL HEALTH TEAM REVIEW**

Date: 04-11-2013

From: Leyla Sahin, M.D.
Medical Officer,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Melissa S Tassinari, PhD.
Acting Team Leader,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Lynne P Yao, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Gastroenterology and Inborn Errors Products

Drug: Procysbi (cysteamine bitartrate); NDA 203389

Applicant: Raptor Therapeutics

Subject: Labeling for Pregnancy and Nursing Mothers

Materials Reviewed: Applicant submission, literature review

Consult Question: Please review the proposed labeling for Pregnancy and Nursing Mothers

INTRODUCTION

Raptor Therapeutics submitted a 505(b) (2) application on March 30th, 2012 for a delayed release formulation for Procysbi® (cysteamine bitartrate) for management of nephropathic cystinosis in children and adults. The referenced innovator drug, Cystagon®, was approved in 1994. The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's (PMHS-MHT) review of the sponsor's proposed labeling for Pregnancy and Nursing Mothers. PMHS-MHT did a literature search on cysteamine use in pregnancy and breastfeeding. This review summarizes available data, and provides conclusions and recommendations regarding Nursing Mothers labeling for Procysbi.

BACKGROUND

Nephropathic cystinosis is a rare autosomal recessive disorder (incidence of 1:100,100 to 200,000), in which there is abnormal transport of cystine out of cellular lysosomes.¹ Clinical features include renal Fanconi syndrome, rickets, growth failure, hypothyroidism, delayed puberty, ocular disease, and central nervous system disease. Without treatment, the natural history of the disease results in death due to renal failure in children under the age of ten. Cysteamine treatment slows progression of the disease, enhances growth, prevents several of the non-renal complications, and increases survival to beyond 50 years of age.

REVIEW OF DATA

Literature Review

There is only one case report of a woman who received cysteamine treatment during pregnancy.² It is not clear whether she was exposed in the first trimester. She delivered a premature infant without any malformations at 33 weeks gestation. There is a case report prior to approval of cysteamine, of a woman with cystinosis who had undergone a renal transplant, and had a successful pregnancy outcome.³

No publications on cysteamine and breastfeeding were found in the literature.

Sponsor's proposed labeling

The following is the sponsor's proposed labeling for Procysbi:

8.1 Pregnancy

Pregnancy Category C.

(b) (4)

¹ Nesterova G, Gahl W. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol* 2008; 23:863-878.

² Haase M et al. Successful pregnancies in dialysis patients including those suffering from cystinosis and familial Mediterranean fever. *J Nephrol* 2006; 19: 677-681.

³ Reiss RA, et al. Successful Pregnancy despite placental cystine crystals in a woman with nephropathic cystinosis. *New England J of Medicine* 1988; 319(4) 223-226.

(b) (4)
There are no adequate and/or well-controlled studies in pregnant women.

PROCYSBI™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether cysteamine is excreted in human milk. (b) (4)

17 PATIENT COUNSELING INFORMATION

DISCUSSION AND CONCLUSIONS

Pregnancy

There is only one case report in the literature regarding the use of cysteamine during pregnancy. The innovator drug, Cystagon, which is the reference drug for this 505(b) (2) application, is labeled pregnancy category C based on adverse developmental effects in the rat at doses less than the recommended human dose. The only studies that were described in the labeling were conducted in the rat. PMHS-MHT had several discussions with DGIEP's toxicology reviewers, Fang Cai, PhD, and David Joseph, PhD, regarding the reproductive toxicology data. Given the absence of new data that would raise a different concern for teratogenic risk, PMHS-MHT agrees, in concurrence with the DGIEP reviewers, that the current regulatory language under Pregnancy, "PROCYSBI™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" adequately reflects the risk –benefit profile regarding use in pregnancy.

PMHS-MHT does not agree with the sponsor's proposal to add language to the Patient Counseling section about (b) (4) as this statement does not reflect the available data. PMHS-MHT also does not agree with the sponsor's proposal to add language to the Patient Counseling section about (b) (4)

Lactation

There are no human data on the use of cysteamine during lactation. A decrease in survival occurred in neonatal rats nursed by (b) (4) receiving cysteamine, and labeling states that serious adverse reactions (e.g., erythema multiforme bullosa, toxic epidermal necrolysis, seizures, gastrointestinal ulceration and bleeding) have occurred in children and adults. Taking the animal lactation data and the potential for serious adverse reactions into consideration, PMHS-MHT recommends against breastfeeding. While current labeling regulations require nursing mothers' language to state that the mother should "discontinue nursing or discontinue drug" when the drug is associated with serious adverse reactions, a woman with nephropathic cystinosis may not have an option to choose between using the drug or breastfeeding. Therefore PMHS-MHT recommends modifying the language to state that nursing is not recommended.

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the labeling, not the amount.

LABELING RECOMMENDATIONS

Recommended additions are underlined and deletions are struck out. These revisions were agreed upon by PMHS-MHT and DGIEP's Toxicology reviewers. See final language pending approval.

~~-----USE IN SPECIFIC POPULATIONS-----~~

- Nursing Mothers: (b) (4) is not recommended (8.3)

8.1 Pregnancy

Pregnancy Category C-

Risk Summary

There are no adequate and/or well-controlled studies (b) (4) in pregnant women.
Cysteamine (administered as cysteamine bitartrate) was teratogenic and fetotoxic (b) (4)
(b) (4) in rats at (b) (4) doses (b) (4)
less than the recommended human maintenance dose (b) (4)

(b) (4)

PROCYSBI™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Embryo-fetal development studies were conducted in rats using oral administration of cysteamine bitartrate, with a dose range of 37.5 to 150 mg/kg/day of cyteamine equivalent (about 0.2 to 0.7 times the recommended human maintenance dose based on body surface area). Cysteamine bitartrate was fetotoxic and produced adverse developmental effects. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly and exencephaly.

8.3 Nursing Mothers

It is not known whether cysteamine is present (b) (4) in human milk. A decrease in survival occurred in neonatal rats nursed by mothers receiving cysteamine (see NONCLINICAL TOXICOLOGY, 13.1). Because many drugs are present excreted in human milk and because of the manifested potential for (b) (4)

serious adverse reactions in nursing infants from cysteamine, nursing is not recommended.

17 PATIENT COUNSELING INFORMATION

(b) (4) Use by pregnant women

(b) (4) - Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Discuss (b) (4) the individual risks and benefits of continuing PROCYSBI™ during pregnancy (b) (4)

Breastfeeding

Breastfeeding is not recommended

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/s/

LEYLA SAHIN
04/11/2013

MELISSA S TASSINARI
04/14/2013

LYNNE P YAO
04/16/2013

MEMORANDUM

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

DATE: April 4, 2013

TO: Donna Griebel, M.D.
Director, Division of Gastroenterology and Inborn
Errors Products
and
Edward D. Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3 (DCPIII)
Office of Clinical Pharmacology

FROM: Xikui Chen, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-389, Cysteamine
Bitartrate Capsules, sponsored by Raptor Therapeutics

At the request of DGIEP and DCPIII, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted a For Cause inspection of the following bioequivalence study:

Study Number: RP103-03
Study Title: "A Randomized Crossover, Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon® in Subjects with Nephropathic Cystinosis"

The audit included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's management and staff.

The For Cause inspection concern was that two adjustments of 33% increase and 25% decrease were made to calculations of cystine concentrations in WBC samples. The study records showed that the 33% increase was due to a dilution step ($4/3=1.33\%$) in the preparation of WBC lysate samples at the clinical sites, and the 25% decrease was due to dilution ($3/4=75\%$) of calibration standards performed at the analytical sites. (b)(4) made calculation corrections for cystine concentrations in updated analytical reports 1085-10154-001.003 and 1085-10153-2.02 dated December 2012.

Analytical Sites:

(b)(4)

The analytical portions of the study were audited at (b)(4)

(b)(4) Following the inspection at (b)(4) Form FDA 483 was issued. (b)(4) response to the observations was received on 3/27/2013 (Attachment 1). The observations, (b)(4) response, and OSI/DBGLPC's evaluations follow.

1. Failure to investigate applying BCA (biscinchronic acid method) to Lowry method factor (1.6999) to calculation of protein concentrations in (b)(4) bioanalytical reports: 1085-10153 and 1085-10154.

In their response, (b)(4) analyzed twenty pooled digested WBC samples from Study PR103-04 for protein content using both the BCA method (SAP.1507) and the Lowry method (SAP.1640) in March 2013, and a factor (slope) 1.39 was observed for protein concentrations between the BCA method and Lowry method, instead of slope 1.00 for identical results.

The factor (slope) 1.6999 used in the calculation of protein concentrations in (b)(4) bioanalytical reports 1085-10153 and 1085-10154 is different from the factor 1.39 obtained in the recent experiments. Because the same factor 1.6999 was applied to protein calculations for both Cystagon and Cysteamine Bitartrate Delayed-release (RP103) Capsule treatments, the impact of different factors on the ratio of protein or cystine/protein

concentrations would be minimal. Thus, the cystine per WBC protein concentrations are usable for the bioequivalence assessments. However, cystine/protein concentration ratios in WBCs can vary with the specific analytical techniques used for measuring cystine and protein in WBCs. If the cystine/protein concentration ratio in WBCs is used to adjust dosing of cysteamine bitartrate, the target concentrations of cystine in WBCs should be established by individual analytical laboratories using local methodology and calibration.

2. Failure to address diluent effects for BCA analytical method SAP.1507 entitled "Total Protein in Human White Blood Cell (WBC) Lysate." Standard calibrators and quality control samples were prepared in water, while WBC was dissolved in 0.1N sodium hydroxide (NaOH) solution in the method. When QC WBC solutions were diluted in water, the recovery of measured protein was about 140%.

(b) (4) responded that the same 0.1 N NaOH should have been used as diluent for calibrators, quality control samples and WBC samples. The data generated in March 2013 show no significant diluent effects when using water or 0.1 N NaOH.

The response from (b) (4) is adequate.

Conclusions:

Following the above inspections, the DBGLPC reviewer recommends the following:

- The data for cysteamine in plasma and cystine alone in white blood cell (WBC) from study RP103-03 are acceptable for review.
- The relative cystine per WBC protein concentrations are usable for the bioequivalence assessments.
- Measured concentrations of cystine/protein in WBCs can vary according to analytical techniques for cystine and protein in WBCs. If cystine/protein concentration in WBCs is used to adjust dosing of cysteamine bitartrate, the target concentrations of cystine/protein in WBCs should be established by individual analytical laboratories using local methodology and calibration.

Final Classifications:

VAI:

VAI:

(b) (4)

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/Chen/CF

OND/ODEIII/DGIEP/Jessica Benjamin/Julie G. Beitz

OMPT/CDER/OTS/OCP/DCPIII/Kristina E. Estes

DET-DO/HFR-CE760/Barbosa

DET-DO/HFR-CE750/Keith J. Jasukaitis (DIB)/Nancy Bellamy (BIMO)

Draft: XC 4/2/2013

Edit: MFS 4/2/2013; SHH 4/2/2013; WHT 4/4/2013

DSI: BE6402; O:\Bioequiv\EIRCover\203389.rap.cys.doc

FACTS: **1487235**

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

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/s/

XIKUI CHEN
04/04/2013

SAM H HAIDAR
04/08/2013

WILLIAM H TAYLOR
04/09/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 203389

Product Name: _____

PMC #1 Description: Include elemental impurities for _____ (b) (4) per USP <232> for the drug product specification.

PMC Schedule Milestones:	Final Protocol Submission:	<u>06/05/2013</u>
	Study/Trial Completion:	<u>06/05/2013</u>
	Final Report Submission:	<u>06/05/2013</u>
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The USP chapter <232> Elemental Impurities – Limits became effective (December 1, 2012) late into the review cycle of NDA 203389. The NDA applicant requested additional time to validate analytical method before the test could be included in the drug product specification.

Implementation of testing for _____ (b) (4) shortly after approval of the NDA is expected not to have a significant impact on the purity of drug product for the following reasons:

- 1) Testing for _____ (b) (4) is included in the drug substance specification. Drug substance constitutes _____ (b) (4) of the drug product.
- 2) The applicant commits to complete the PMC by June 5, 2013.

2. Describe the particular review issue and the goal of the study.

See above

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Include elemental impurities for (b) (4) per USP <232> for the drug product specification. Analytical method validation data as well as an updated drug product specification will be provided.

5. To be completed by ONDQA/OBP Manager:

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

Yes.

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.*

(signature line for BLAs only)

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/s/

JANE L CHANG
04/01/2013
CMC PMC

MOO JHONG RHEE
04/01/2013
Chief, Branch IV

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203389 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: RP103, cysteamine bitartrate delayed release capsules Dosage Form: capsules Strengths: 25mg, 75mg		
Applicant: Raptor Therapeutics Agent for Applicant (if applicable):		
Date of Application: 3/30/2012 Date of Receipt: 30/30/2012 Date clock started after UN:		
PDUFA Goal Date: 1/30/2013	Action Goal Date (if different):	
Filing Date: 5/29/2012	Date of Filing Meeting: 5/9/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): treatment of nephropathic cystinosis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 103694				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , 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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) 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...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>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.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?			X	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)			X	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 1/28/2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 10/25/2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 9, 2013

BLA/NDA/Supp #: NDA 203389

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: RP103, cysteamine bitartrate delayed release capsules

DOSAGE FORM/STRENGTH: capsules, 25mg and 75mg

APPLICANT: Raptor Therapeutics

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of nephropathic cystinosis

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Wes Ishihara	N
Cross-Discipline Team Leader (CDTL)	Lynne Yao		Y
Clinical	Reviewer:	Carla Epps	Y
	TL:	Lynne Yao	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Dilara Jappar	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fang Cai	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Jane Chang	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Justin Earp, Karen Riviere		Y
Other attendees	Donna Griebel, Andrew Mulberg		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority:</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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APPEARS THIS WAY ON ORIGINAL



Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JESSICA M BENJAMIN
02/21/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 4, 2012

TO: Jessica Benjamin, Project Manager
Carla Epps, M.D., Medical Reviewer

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-389

APPLICANT: Raptor Therapeutics, Inc.

DRUG: cysteamine bitartrate delayed-release (Procysbi)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Management of nephropathic cystinosis in children and adults.

CONSULTATION REQUEST DATE: June 7, 2012

Inspection Summary Goal Date: October 31, 2012

Division Action Goal Date: January 16, 2013

I. BACKGROUND:

Cystinosis is an autosomal recessive error of metabolism in which the transport of cystine out of lysosomes is reduced or absent. Nephropathic cystinosis is a rare disease (about 500 in the U.S.), characterized by the accumulation of cystine and formation of crystals damaging various organs especially the kidney, leading to renal tubular Fanconi Syndrome and progressive glomerular failure, with end stage renal failure by the end of the first decade of life. Patients experience growth failure, rickets, and photophobia.

“Cytagon” (cysteamine bitartrate) became available as a treatment for cystinosis in 2007. Cysteamine reacts within lysosomes to convert cystine into cysteine and cysteine-cysteamine which can exit the lysosomes. Cytagon requires administration every 6 hours around the clock. This causes poor compliance and the need for earlier hemodialysis and kidney transplantation. The new drug is a delayed release form to be administered twice a day.

The most common reported adverse events of cysteamine were vomiting, anorexia, fever, diarrhea, lethargy, and rash. The less common adverse reactions are CNS symptoms, encephalopathy and gastrointestinal tract symptoms, leucopenia, abnormal liver functions, headache, tinnitus, diplopia and blurry vision.

Inspections of the following two protocols were requested by the review division and sites were chosen because of high enrollment in the studies:

1. RP103-03: “A Randomized, Crossover, Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) Compared to Cystagon[®] in Subjects with Nephropathic Cystinosis”
2. RP103-04: “A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Cystinosis”

II. RESULTS (by Site):

Name of CI/ Location/ Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Larry Greenbaum, M.D. Atlanta, GA-Site 03	RP103-03, 12 Subjects RP103-04, 11 Subjects	September 25- October 4, 2012	NAI
Patrick Niaudet, M.D Paris, France-Site 06	RP103-03, 6 Subjects RP103-04, 6 Subjects	November 5-9 2012	NAI (Pending)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Larry Greenbaum, M.D.

Atlanta, GA, Site # 03

- a. **What was inspected:** The field investigator and I reviewed all study records for both protocols. For Protocol RP103-03, 12 subjects were enrolled, and one was terminated at Month 2 visit due to inability to tolerate the drug. For Protocol RP103-04, 11 subjects were enrolled. Of these, 9 participated in Protocol RP103-03. The review included eCRFs, vital signs, physical exams, ECGs, lab reports, data listings, drug accountability records, and adverse events.
- b. **General observations/commentary:** Subject #010/MS in Protocol RP103-04 had been hospitalized for stomach pain in (b) (6), but was only recently known to the site before our inspection. Results of WBC cystine assessments for Protocol RP103-03 were obtained from the lab and compared with the data listings and found to be accurate. For Protocol RP103-04, WBC cystine levels were accessible to the site through an online source and the information was kept in a web-based database. The inspection revealed no violations of federal regulations.
- c. **Assessment of data integrity:** The data generated at this site are reliable and can be used in support of the NDA.

2. **Patrick Niaudet, M.D.**
Paris, France

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

- a. **What was inspected:** For Protocol RP103-03, six subjects enrolled and all completed the study. For Protocol RP103-04, seven subjects enrolled and six subjects completed the study because one subject did not tolerate Cystagon. The field investigator reviewed the records of all subjects in both studies. The review included consent forms, subject diaries, primary and secondary efficacy parameters.
- b. **General observations/commentary:** Data listings provided were found to be comparable to source documents with no discrepancies. All adverse reactions were reported and there were no protocol deviations observed. The review revealed no violations of federal regulations
- c. **Assessment of data integrity:** The data generated at this site are reliable and can be used in support of the NDA

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were inspected for this NDA. The classification for Dr. Greenbaum's site is NAI, as is the preliminary classification for Dr. Niaudet's site. The data generated at the two sites inspected are reliable and can be used in support of the NDA.

An addendum to this clinical inspection summary will be forwarded to the Review Division should there be a change in the final classification, or if additional observations of clinical and regulatory significance are discovered after reviewing the EIR of Dr. Niaudet in Paris, France (Site # 06).

{ See appended electronic signature page }

Khairy Malek, M.D., PhD.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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/s/

KHAIRY W MALEK
12/07/2012

SUSAN LEIBENHAUT
12/07/2012

SUSAN D THOMPSON
12/07/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203389

Name of Drug: cysteamine bitartrate delayed-release capsules (RP103)

Applicant: Raptor Therapeutics Inc.

Labeling Reviewed

Submission Date: 3/30/2012

Receipt Date: 3/30/2012

Background and Summary Description

This is a 505(b)(2) NDA for cysteamine bitartrate delayed-release capsules (RP103) for the management of nephropathic cystinosis in children and adults. The reference drug and the basis for this application is Cystagon, NDA 20392. Cysteamine bitartrate delayed-release capsules (RP103) was granted orphan designation on 24 October 2006.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by June 29, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**
 - A horizontal line must separate the TOC and FPI.
 - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
 - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
 - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
 - Must include a brief, concise summary of critical information and cross-reference to detailed

discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Statement not included

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Statement not included

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”

- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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JESSICA M BENJAMIN
12/03/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 22, 2012

Reviewer: Anne Crandall Tobenkin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH.
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s): Procysbi (Cysteamine Bitartrate) Delayed-release Capsules

Strength(s): 25 mg and 75 mg

Application Type/Number: NDA 203389

Applicant/sponsor: Rapture

OSE RCM #: 2012-910

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

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Procysbi (NDA 203389) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the April 9, 2012 proprietary name submission. The NDA was submitted in accordance with section 505(b)(2) with Cystagon as the Reference Listed Drug. The proprietary name, Procysbi, is evaluated in OSE review # 2012-908.

Table 1: Procysbi Product Characteristics	
Product	Procysbi (NDA 203389)
Established Name	Cysteamine Bitartrate
Indication of Use	Management of nephrotic cystinosis
Route of Administration	Oral
Dosage Form	Delayed-release capsule
Strength	25 mg, 75 mg
Dose * Maintenance dose should be reached after 4 to 6 weeks of incremental dosage increases	<p>(b) (4)</p> <p><u>Starting dose:</u> (b) (4) by mouth every 12 hours</p> <p><u>Maintenance dose:</u> 650 mg/ m² by mouth twice daily</p> <p>(b) (4)</p>
How Supplied	25 mg: bottles of 60 capsules 75 mg: bottles of 250 capsules
Storage	Protect from light and moisture
Container and Closure Systems	Procysbi should only be dispensed in the original packaging
Distribution	Controlled distribution system using single specialized pharmacy and distributor

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Cystagon (Cysteamine) medication error reports because Cystagon is the same active ingredient with a different release mechanism. We also reviewed the labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 2.

Date	No date limitation
Drug Names	Active ingredient: Cysteamine Trade name: Cystagon Verbatim term: Cystago%
MedDRA Search Strategy	HLGT: Medication Errors HLT: Product Quality Issues NEC HLT: Product Packaging Issues HLT: Product Label Issues

The AERS database search identified three reports. Each report was reviewed for relevancy and duplication. After individual review, all three cases were excluded for the following reasons: adverse event with Cystagon therapy unrelated to a medication error, overdose due to child giving sibling drug product, and overdose with no explanation.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on May 24, 2012 for additional cases and actions concerning Cysteamine. No articles were identified that involved Cystamine medication errors.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 9, 2012 (Appendix A)
- Insert Labeling submitted April 9, 2012 (no image)

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

2.4 PREVIOUSLY COMPLETED REVIEWS

No label reviews were completed by DMEPA, however three name reviews were (OSE reviews # 2010-2552, # 2011-2521 and # 2012-908 were completed and recommendations were made regarding strength and dose correlation which is further discussed in Section 3.

3 MEDICATION ERROR ASSESSMENT

Previous reviews noted that the proposed established name (Cysteamine bitartrate) and proposed strengths (25 mg and 75 mg) are incongruent because the established name is expressed in terms of the salt of the active moiety and the strengths are based on the free base of the active moiety. The currently marketed Cysteamine bitartrate product (Cystagon) also expresses the established name and strengths in the same manner. However, this presentation is inconsistent with the USP salt nomenclature policy, therefore, we defer to the expertise of ONDQA regarding this issue.

As stated above, there are only 2 strengths being proposed for this product. The usual maintenance doses for pediatric and adult patients can range between [REDACTED] (b) (4) twice daily. As a result, a patient will have to administer several capsules to obtain a desired dose, which may put a significant burden on a patient and possibly reduce adherence to therapy. For example, to obtain a dose of 600 mg, a patient would need to administer 24 capsules of 25 mg strength or 8 capsules of 75 mg strength. Additionally, the doses require rounding in order to deliver the dose with the available strengths. Thus, DMEPA recommends developing higher strengths of Cysteamine Bitartrate Delayed-release Capsules strengths to accommodate the need for larger doses and to decrease the burden. However, these new strengths should not overlap with the reference listed product, Cystagon, which is an immediate release formulation containing the same active ingredient. Creating overlapping strengths between the immediate release and extended-release formulation may result in wrong drug errors if products are ordered by the established name only because the fact that one product is immediate-release and the other is delayed-release may be overlooked.

The Applicant proposed a single distribution through a specialty pharmacy for Procysbi. Procysbi, per the Applicant's instructions, must be dispensed in the original container. However the containers are only available in two counts, 60 capsules or 250 capsules. In order to accommodate the weight-based doses, practitioners may be inclined to splitting the bottles to accommodate the calculated dose for a 30 or 60 day supply. For example, if the patient is prescribed 1400 mg twice daily, a prescription for a 30 day supply would be 900 capsules. Therefore, if the intention is to dispense in the original containers, more container sizes should be available to dispense directly to patients. Another concern with the proposed product label is the proposed 25 mg and 75 mg strength container labels exhibit [REDACTED] (b) (4)

[REDACTED] making the proposed strengths difficult to differentiate and may result in wrong dose administration. It is very likely that patients will be prescribed both strengths at some time during the titration phase, making it imperative that both the labels and capsule for each strength be well differentiated to ensure patients can correctly choose the strength and corresponding number of capsules. Also, the manufacturer

information on the principal display panel is more prominently displayed than the product names and strength, increasing the visual similarities between the two proposed strengths.

4 CONCLUSIONS

As stated in previous OSE proprietary name reviews, the Applicant should consider marketing strengths that better correlate with the recommended dose so that patients are not required to consume a large number of capsules for the typical maintenance dose. Also, because the capsules must be dispensed in the original packaging, the Applicant should consider marketing more sizes to better accommodate the prescribed number of capsules. Additionally, DMEPA concludes that the proposed labels and capsule presentations are unacceptable and should be revised so that the strengths are more visually differentiated for both the capsules and the labels, as well as relocate and decrease information on the principal display panel to better convey safety information associated with the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA/ANDA/supplement:

A. Comments to the Division

1. General Comments

- a) The proposed established name and strengths are incongruent because the established name is expressed in terms of the salt of the active moiety and the strength is based on the free base of the active moiety. After discussion with the ONDQA reviewer, ONDQA determined that it was best to keep the established name and strengths as proposed because it aligns with the regular release product that is currently marketed (Cystagon). We concur with ONDQA.
- b) DMEPA recommends developing higher strengths of Procysbi capsules to better accommodate the need for larger doses and to decrease pill burden. However, these new strengths should not overlap with the reference listed product, Cystagon, because both Cystagon and Procysbi contain the same active ingredient and if products are ordered by the established name, the fact that one product is immediate-release and the other is delayed-release may be overlooked, which may result in the wrong drug error.
- c) As currently proposed, Procysbi must be dispensed in the original bottle. However, each strength is only available in one bottle size: 25 mg (60 capsules) or 75 mg (250 capsules). In order to accommodate the weight based doses, pharmacists may be inclined to splitting the bottles to accommodate the calculated dose for a 30 or 60 day supply. For example, if the patient is prescribed 1400 mg twice daily, a prescription for a 30 day supply would be 900 capsules, resulting in one bottle being split. Therefore, if the intention is to dispense in the original containers, more container sizes with greater numbers of

capsules should be available for both strengths in order to dispense directly to patients.

2. Insert Labeling

- a) Revise the dosing instructions in the Dosage and Administration Section so that the physicians are presented the dose broken up into the milligrams every 12 hours rather than (b) (4)
- b) Revise the presentation of the dosing recommendations (weight in pounds, mg of Procysbi every 12 hours) so that it appears in a table with grid lines to enhance the visibility of weight and corresponding mg dose.
- c) Highlight that patients should first be stabilized on the regular release formulation before switching to the delayed-release formulation.
- d) Include in Section (b) (4) “How should I store Procysbi”, that capsules should be stored in the original container in order to ensure that the capsules are not exposed to light or moisture.
- e) Remind providers in the Dosage and Administration Section that they should order capsules in numbers of 60 (for 25 mg strength) or 250 (for 75 mg strength) to ensure that the capsules are dispensed in the original container.

B. Comments to the Applicant

1. Product Design

- a) Per the “How Supplied” Section of the insert, the 25 mg and 75 mg strengths are (b) (4)

2. Container Label

- a) (b) (4) To prevent selection errors, increase the visual differentiation of the proposed strengths using a unique color scheme for each strength. The colors chosen can also be reflected in the capsule color to ensure improved strength identification.
- b) Relocate the strength so that it appears beneath the established name.
- c) Relocate the quantity statement so that it appears toward the bottom of the principal display panel and away from the product strength.

- d) Remove the ^{(b) (4)} of the capsule on the principal display panel that appears beneath the strength, ^{(b) (4)}
- e) Relocate the “Dispense only in original packaging” statement so that it appears on the principal display panel and highlight the information by color blocking it.
- f) Decrease the prominence of the “Raptor” logo and the address by decreasing the size of the letters and removing the ^{(b) (4)}. Additionally, relocate this information to the back panel so that more important safety information is conveyed on the principal display panel
- g) Bold the “Delayed-release” statement to ensure that this difference between Procysbi (Cysteamine Bitartrate) Delayed Release Capsules and Cystagon (Cysteamine Bitartrate) is highlighted.
- h) Add the statement, ‘Capsules should be swallowed whole. Do not crush or chew’ and locate it below the dosage form on the principal display panel.
- i) Consider including that Procysbi is taken twice daily in the usual dose statement if space permits, because this is a delayed release formulation of a currently marketed product that is taken four times daily.
- j) If additional space is needed on the side panel, consider revising the statement that reads, “KEEP THIS AND ALL....” from all caps to title case.

If you have further questions or need clarifications, please contact Franklin Stephenson, OSE project manager, at 301-796-3872.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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/s/

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KELLIE A TAYLOR
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