

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203389Orig1s000**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

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

**DATE:** April 24, 2013

**TO:** Review #1 of NDA 203389

**FROM:** Jane Chang, Ph.D.  
Review Chemist, ONDQA

**SUBJECT:** Final ONDQA Recommendation on NDA 203389  
Procysbi (cysteamine bitartrate) Delayed-release Capsules

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**SUMMARY**

In NDA 203389 CMC Review #1 dated 05-Mar-2013, it was recommended that the NDA was not ready for approval in its present form because labeling issues were not resolved.

Subsequently, the applicant provided a revised package insert labeling, in which revisions were made to sections 'Highlights', 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling' per ONDQA's recommendation. In addition, the capsule color for the 25 mg strength has been changed [REDACTED] <sup>(b) (4)</sup> to a single-tone color in response to DMEPA's recommendation dated 13-Mar-2013. Consequently, revised drug product sections, including the drug product specification, and container labels were provided in the 28-Mar-2013 and 24-Apr-2013 amendments, respectively. The revised labeling and drug product specification are satisfactory from the ONDQA perspective.

A post marketing commitment for inclusion of elemental impurities for the drug product specification, which will be completed by June 5, 2013, remains unchanged (See PMR/CMC Development Template dated 01-Apr-2013).

**RECOMMENDATION**

This NDA is now recommended for approval from the ONDQA perspective.

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### Review Notes

Labeling issues were identified in CMC Review #1 dated 05-Mar-2013 (see pages 9 and 149-155). Subsequently, the applicant provided a revised package insert labeling to Project Manager, Ms. Jessica Benjamin, who then placed it in the eRoom on April 12, 2013. The revised labeling incorporated this reviewer's recommendations for sections 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling' (see Review #1). In addition, the capsule color of 25 mg strength has been changed to a single-tone color of light blue opaque for cap and body, (b) (4)

This change was made in response to the DMEPA's recommendation dated 13-Mar-2013 to avoid color similarity between the two strengths. Subsequently, revised drug product sections, including the drug product specification, and container labels were provided in the 28-Mar-2013 and 24-Apr-2013 amendments, respectively.

A post marketing commitment for inclusion of elemental impurities for the drug product specification, which will be completed by June 5, 2013, remains unchanged (See PMR/CMC Development Template dated 01-Apr-2013).

The updated information is summarized below.

## **I. PACKAGE INSERT (placed in eRoom on April 12, 2013)**

### **1. "Highlights" Section**

**PROCYSBI (cysteamine bitartrate) delayed-release capsules, for oral use**  
**Initial U.S. Approval: 1994** (b) (4)

-----**DOSAGE FORMS AND STRENGTHS**-----

Delayed-release capsules: 25 mg and 75 mg

*Reviewer's Assessment: The issue on established name and expression of strengths for Procysbi was detailed in CMC Review #1 (pages 149-150). This issue was discussed in the 3/12/2013 NDA wrap-up meeting, where an agreement was reached by the review team (see Attachment on page 12). That is, the same approach as the approved product, Cystagon, for the established name and expression of strength will be adopted for Procysbi. The name of the salt, i.e. cysteamine bitartrate, will be used as the established name and the strength of Procysbi will be expressed as cysteamine free base. The main consideration in adopting the same established name and expression of strength as Cystagon is to prevent confusion and potential medical errors. Procysbi, once approved, will be prescribed for a very small population, who likely are already taking Cystagon. The established name is an exception to the USP salt policy as allowed by MAPP 5021.1, under Background, Section C.2.a.*

### **2. Prescribing Information**

#### **a. Section 2 Dosage and Administration**

##### **2.3 Administration Options**

**PROCYSBI (cysteamine bitartrate) delayed-release capsules – Oral Administration**

- PROCYSBI should be swallowed whole.
- Alternatively, for patients who have difficulty swallowing capsules, PROCYSBI (cysteamine bitartrate) delayed-release capsules can be opened and administered as follows:
  - Open capsule.
  - Sprinkle intact granules on approximately 4 ounces (1/2 cup) of applesauce or berry jelly.
  - Eat mixture within 30 minutes of preparation.
- PROCYSBI may also be emptied into a small volume of either orange juice or apple juice:
  - Mix or Sprinkle intact granules into a small volume of either orange juice or apple juice (approximately 4 ounces (½ cup)).
  - Shake gently for 5 minutes then administer by spoon or cup within 30 minutes.

**PROCYSBI Feeding tube Administration**

- For patients who have a 12 French or larger (b) (4) gastrostomy (G)-tube, (b) (4) in place, PROCYSBI can be administered as follows:
  - Open capsule.
  - Mix intact granules into approximately 4 ounces (1/2 cup) of applesauce.
  - Administer mixture via feeding tube within 30 minutes.
  - Flush with approximately 8 ounces (1 cup) of orange juice or apple juice to clear the tube.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

*Reviewer's Comments: In CMC Review #1 (page 68), data were included to support the choice of food (i.e. applesauce or berry jelly) for sprinkling option and of liquid (i.e. orange juice or apple juice) as well as the hold time of NMT 30 minutes. An in vitro study was also conducted to support administration of Procysbi granules in applesauce through a feeding tube of internal diameter of 6 mm (CMC Review #1, page 68). In the 4/23/2013 amendment, the applicant stated that Procysbi granules in applesauce have been administered successfully via g-tubes of 12 French to 18 French to several subjects in Study RP103-04.*

**b. Section 3 Dosage Forms and Strengths**

- Each 25 mg delayed-release capsule contains 74 mg cysteamine bitartrate, equivalent to 25 mg cysteamine. The capsules are light blue opaque cap imprinted with 'Raptor' logo in white ink and light blue opaque body imprinted with '25 mg' in white ink.
- Each 75 mg delayed-release capsule contains 221 mg cysteamine bitartrate, equivalent to 75 mg cysteamine. The capsules are dark blue opaque cap

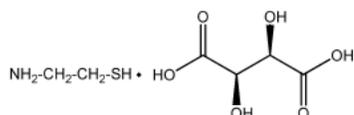
imprinted with 'Raptor' logo in white ink and light blue opaque body imprinted with '75 mg' in white ink.

*Reviewer's Assessment:* This section is satisfactory. This section has been revised per this reviewer's recommendation (see Review #1, page 150). Adequate information is included for dosage forms, strengths, and description of identifying characteristics of capsules, such as the color and inscriptions. The amounts of cysteamine bitartrate as well as the label strength (in cysteamine) for each strength of capsules are included. As stated previously, the capsule color of 25 mg strength has been changed [REDACTED] <sup>(b) (4)</sup> [REDACTED] to a single-tone color of light blue opaque for cap and body to avoid the color similarity between 25 mg and 75 mg strengths.

**c. Section 11 Description**

PROCYSBI (cysteamine bitartrate) delayed-release capsules for oral administration, is a cystine depleting agent which lowers the cystine content of cells in patients with nephropathic cystinosis, an inherited defect of lysosomal transport.

PROCYSBI contains the bitartrate salt of cysteamine. The chemical name for cysteamine bitartrate is ethanethiol, 2-amino, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt). Cysteamine bitartrate is a highly water soluble white powder with a molecular weight of 227.24 and the molecular formula  $C_2H_7NS \cdot C_4H_6O_6$ . It has the following chemical structure:



Each 25 mg delayed-release capsule contains 74 mg cysteamine bitartrate, equivalent to 25 mg cysteamine. Each 75 mg delayed-release capsule contains 221 mg cysteamine bitartrate, equivalent to 75 mg cysteamine. PROCYSBI (cysteamine bitartrate) delayed-release capsules contain the following inactive ingredients: microcrystalline cellulose, Eudragit<sup>®</sup> L 30 D-55, hypromellose, talc, triethyl citrate, sodium lauryl sulfate, and purified water. Capsule shell ingredients are gelatin, titanium dioxide, blue ink and white ink.

*Reviewer's Assessment:* This section has been revised per this reviewer's recommendation (see Review #1, pages 152-153). The information is acceptable.

<i>Item</i>	<i>Comments on the Information Provided in NDA</i>	<i>Conclusions</i>
<i>Proprietary name and established name</i>	<i>Procysbi Established name, cysteamine bitartrate, was provided.</i>	<i>Satisfactory</i>
<i>Dosage form and route of administration</i>	<i>capsule, oral</i>	<i>Satisfactory</i>
<i>Active moiety expression of strength with equivalence statement</i>	<i>The following statement is included: “Each 25 mg delayed-release capsule contains 74 mg cysteamine bitartrate, equivalent to 25 mg cysteamine. Each 75 mg delayed-release capsule contains 221 mg cysteamine bitartrate, equivalent to 75 mg cysteamine.”</i>	<i>Satisfactory</i>
<i>Inactive ingredient information</i>	<i>All inactive ingredients are listed as follows: microcrystalline cellulose, Eudragit® L 30 D-55, hypromellose, talc, triethyl citrate, sodium lauryl sulfate, and purified water. Capsule shell ingredients are gelatin, titanium dioxide, blue ink and white ink They are not listed in alphabetical order, but since it is not an OTC product, it is acceptable.</i>	<i>Satisfactory</i>
<i>Pharmacological/ therapeutic class per 21 CFR 201.57(c)(12)(E)</i>	<i>A cystine depleting agent</i>	<i>Satisfactory</i>
<i>Chemical name, structural formula, molecular weight</i>	<i>Structural formula, molecular weight, and chemical name are provided correctly.</i>	<i>Satisfactory</i>

Conclusion: **Satisfactory**

#### **d. Section 16 How Supplied/Storage and Handling**

##### How Supplied

- **25 mg Delayed-release Capsule:** A hard gelatin capsule with light blue opaque cap imprinted with Raptor Logo in white ink and light blue opaque body imprinted with “25 mg” in white ink, supplied as bottle of 60 capsules (NDC 4966-3001-06).
- **75 mg Delayed-release Capsule:** A hard gelatin capsule with dark blue opaque cap imprinted with Raptor Logo in white ink and light blue opaque body imprinted with “75 mg” in white ink, supplied as bottle of 250 capsules (NDC 4966-3002-25).

##### Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Dispense only in original packaging. Do not subdivide or repackage. Do not remove desiccant or oxygen absorber from the container. Keep bottles tightly closed in a dry place.

*Reviewer's Assessment:* This section has been revised per this reviewer's recommendation (see Review #1, pages 154-155). In addition, the capsule color of 25 mg strength has been revised to a single-tone color of light blue opaque for cap and body.

<b>Item</b>	<b>Comments on the Information Provided in NDA</b>	<b>Conclusions</b>
Strength of dosage form in metric system	Strengths are correctly described as 25 mg and 75 mg per capsule	<b>Satisfactory</b>
Units of dosage form	Available units are correctly described as 60 capsules per bottle for 25 mg and 250 capsules for 75 mg	<b>Satisfactory</b>
Identification of dosage forms, shape, color, coating, scoring, imprinting, NDC number	The identification of the dosage form is correctly described as follows: 25 mg A hard gelatin capsule with light blue opaque cap imprinted with Raptor Logo in white ink and light blue opaque body imprinted with "25 mg" in white ink, supplied as bottle of 60 capsules (NDC 4966-3001-06) 75 mg: A hard gelatin capsule with dark blue opaque cap imprinted with Raptor Logo in white ink and light blue opaque body imprinted with "75 mg" in white ink, supplied as bottle of 250 capsules (NDC 4966-3002-25)	<b>Satisfactory</b>
Special handling (e.g., protect from light)	Dispense only in original packaging. Do not subdivide or repack. Do not remove desiccant or oxygen absorber from the container. Keep bottles tightly closed in a dry place.	<b>Satisfactory</b>
Storage condition	Storage condition is described as "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature]. Protect from light and moisture."	<b>Satisfactory</b>

**Conclusion:** *Satisfactory*

**e. Manufacturer's or Distributor's name**

**Manufactured for:**  
Raptor Pharmaceuticals Inc.  
9 Commercial Blvd, Suite 200  
Novato, CA 94949



*Reviewer's Assessment:* The information in this section, which is provided at the end of Prescribing Information, remains the same as that provided in the original submission.

**Conclusion:** *Satisfactory*

## II. CONTAINER LABELS

The revised container labels were provided in the 4/24/2013 amendment per DMEPA's information request dated 3/13/2013. The labels are shown below.



*Reviewer's Assessment: The (b) (4) has been deleted from the container labels. Per (b) (4) is requested, but not required to appear on all drug labels and all drug labeling. All other pertinent information remains unchanged. From CMC perspective, the container labels remain acceptable.*

## III. MODULE 3 DRUG PRODUCT SECTION

Revised 3.2.P.1, 3.2.P.4.1, and 3.2.P.5.1 sections were provided in the 3/28/2013 amendment to update the capsule color change for the 25 mg strength.

### 1. Section 3.2.P.1

The capsule color for the 25 mg strength has been revised (b) (4) to a single-tone color of light blue opaque for cap and body. Thus, the 25 mg capsules are described as:

“The 25 mg strength size 3 capsule is a single-tone light blue opaque capsule (body and cap). The body is imprinted with ‘25 mg’ in white ink and the cap is imprinted with ‘Raptor’ logo in white ink.”

The composition of hard gelatin capsule, size 3 is also updated as following (the revisions are reflected in the **bold** font):

**Table 1: Hard Gelatin Capsule Composition, Size 3**

Ingredient	Function	Composition	Reference	
<b>Body</b>				
FD&C Blue (b)(4)		(b)(4)	21 CFR	
Titanium Dioxide			21 CFR, USP/NF	
Gelatin			USP/NF	
<b>Cap</b>				
FD&C Blue (b)(4)				21 CFR
Titanium Dioxide				21 CFR, USP/NF
Gelatin				USP/NF

**2. Section 3.2.P.4.1**

The revised specification for gelatin capsule size 3 is summarized below (the revisions are reflected in **bold** font).

**Table 2: Hard Gelatin Specification**

Test	Acceptance Criteria
Appearance	Satisfactory
Color	<b>Light Blue Opaque Cap and Body</b>
Printing	Body – “25 mg” in White Ink Cap – “Raptor” in White Ink
Identity	Gelatin (per NF monograph): Positive Titanium Dioxide: Positive
Size	No. 3
Weight	45-51 mg/capsules (mean weight) Target weight: (b)(4)/capsule
Acid Solubility	Passes Test

**3. Section 3.2.P.5.1**

The revised drug product specification is shown below (the revisions are highlighted in **bold** font).

**Table 3: RP103 Drug Product Specification**

Test	Acceptance Criteria	Method
Appearance	25 mg (b)(4) <b>Light</b> blue opaque cap imprinted with ‘Raptor’ logo in white ink and light blue opaque body imprinted with ‘25 mg’ in white ink, filled with white to off-white beads	P14100 (visual)
	75 mg (b)(4) <b>Dark</b> blue opaque cap imprinted with ‘Raptor’ logo in white ink and light blue opaque body imprinted with ‘75 mg’ in white ink, filled with white to off-white beads	

**Table 3 Continued**

Test	Acceptance Criteria	Method
Identity by NIR	The near-infrared reflectance spectrum exhibits absorption bands at the required locations and within the specified ranges	870210
Identity by HPLC	The retention time of the main sample peak matches within $\pm 0.5$ min. of main standard peak retention time	883011
Uniformity of dosage units	Meets USP <905> Uniformity of Dosage Units	
Assay	90.0 – 110.0% Label Claim	
Moisture	Release: (b) (4) Stability: (b) (4)	134610
Dissolution	Acid Stage: Meets USP <711> for Delayed Release Dosage Forms Buffer Stage: Not less than (b) (4) (Q) of the label claim of cysteamine is dissolved after 20 minutes in sodium phosphate buffer, pH 6.8	929946
Microbial Limits Total Aerobic Microbial Counts Total Yeasts and Molds Counts <i>Escherichia coli</i>	(b) (4)  Absent/g	B869120
Related Substances Cystamine (w/w%) Other specified impurities	RRT  Release (b) (4) Stability (b) (4)	(b) (4)
[Redacted Content]		883011

*Reviewer's Assessment: The information is acceptable. The change in capsule color for the 25 mg strength to a single-tone color will not have any negative impact on the purity and quality of the drug product because the same light blue color has been used for the capsule body for the clinical and primary stability batches.*

## IV. ATTACHMENT – EMAIL CORRESPONDENCE

**Chang, Jane**

---

**From:** Dimick, Lara L  
**Sent:** Tuesday, March 12, 2013 3:41 PM  
**To:** Chang, Jane  
**Subject:** RE: Established name for Procysbi NDA 203389

agree

*Lara*

*Lara Dimick-Santos, MD, FACS  
Medical Team Leader (Acting)  
Liver and Inborn Errors of Metabolism Team  
FDA/CDER/OND/ODE3/DGIEP  
White Oak - Building 22, Room 5112  
O - 301-796-4843*

(b) (6)

*Lara.Dimick@fda.hhs.gov*

---

**From:** Chang, Jane  
**Sent:** Tuesday, March 12, 2013 3:40 PM  
**To:** Mulberg, Andrew; Dimick, Lara L; Epps, Carla L.; Korvick, Joyce A; Owens, Lissa; Merchant, Lubna; Benjamin, Jessica  
**Cc:** Rhee, Moo Jhong; Kowblansky, Marie  
**Subject:** Established name for Procysbi NDA 203389

Hi, all,

I would like to recap what we have agreed on the established name and expression of strength for Procysbi in today's team meeting.

**The same approach as the approved product, Cystagon, for the established name and expression of strength will be adopted for Procysbi. That is, the name of the salt, i.e. cysteamine bitartrate, will be used as the established name and the strength of Procysbi will be expressed as cysteamine free base.**

The main consideration in adopting the same established name and expression of strength as Cystagon is to prevent confusion and potential medical errors. Procysbi, once approved, will be prescribed for a very small population, who likely are already taking Cystagon.

Jane

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE L CHANG  
04/24/2013

MOO JHONG RHEE  
04/24/2013  
Chief, Branch IV

# **NDA 203389**

**Procysbi (cysteamine bitartrate) Delayed-release Capsules  
25 mg and 75 mg**

**Raptor Pharmaceuticals Inc.**

**Jane L. Chang, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV**

**For Division of Gastroenterology and Inborn Errors Products  
HFD-180**

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 203389
2. REVIEW #: 1
3. REVIEW DATE: 05-Mar-2013
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
1/28/2010 EOP2 Meeting Minutes	25-Feb-2010
10/25/2011 Pre-NDA Meeting Minutes	22-Nov-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	30-Mar-2012
Amendment (Quality)	30-Apr-2012
Amendment (Quality)	29-May-2012
Amendment (Labeling)	26-Jun-2012
Amendment (Quality)	05-Sep-2012
Amendment (Quality)	07-Sep-2012
Amendment (Quality)	05-Oct-2012
Amendment (Quality)	09-Oct-2012
Amendment (Quality)	16-Oct-2012
Amendment (Quality)	01-Nov-2012
Amendment (Quality)	26-Nov-2012
Amendment (Quality)	30-Nov-2012
Amendment (Quality)	14-Dec-2012
Amendment (Quality)	19-Dec-2012
Amendment (Quality)	28-Jan-2013
Amendment (Labeling)	30-Jan-2013
Amendment (Quality)	13-Feb-2013
Amendment (Quality)	20-Feb-2013

## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Raptor Therapeutics Inc.  
Address: 9 Commercial Blvd Suite 200  
Novato, CA 94949  
Representative: Yvonne Kim, Director, Regulatory Affairs  
Telephone: 510-304-8770

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Procysbi  
b) Non-Proprietary Name (USAN): cysteamine bitartrate\*  
c) Code Name/# (ONDQA only): N/A  
d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5 (new formulation, per MAPP 7500.3)
  - Submission Priority: S

*\*Reviewer's Note: Only cysteamine and cysteamine hydrochloride are included in USAN Dictionary.*

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: a cystine depleting agent

## 11. DOSAGE FORM: capsules

## 12. STRENGTH/POTENCY: 25 mg and 75 mg as cysteamine free base

## 13. ROUTE OF ADMINISTRATION: oral

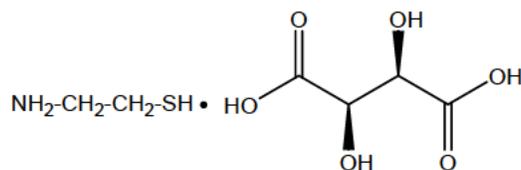
14. Rx/OTC DISPENSED: Y Rx    OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

   SPOTS product – Form Completed

Y Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



Molecular Formula: C<sub>2</sub>H<sub>7</sub>NS • C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>

Molecular Weight: 227.24

Molecular Weight of cysteamine free base: 77.15

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1/29/2013	By J. Chang
	III		1	Adequate	9/10/2012	By J. Chang	
	III		4	N/A	N/A	See page 123	
	III		3	Adequate	6/16/2011	By G. Lunn	
	IV		4	N/A	N/A	See pages 81 and 82	
	III		3	Adequate	3/21/2012	By G. Holbert	
	III		7	N/A	N/A	Non-product contact	
	III		1	Adequate	10/26/2012	By J. Chang	
	III		7	N/A	N/A	Non-product contact	
	III		4	N/A	N/A	See page 123	
	III		1	Adequate	9/17/2012	By J. Chang	

\*Referenced by the holder of DMF (b) (4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	103694	cysteamine bitartrate capsules
IND	74146	cysteamine bitartrate/Cystagon Enteric Coating

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	9/24/2012	Rokhsana Safaai-Jazi
Pharm/Tox	N/A		
Biopharm	Approval	2/14/2013	Kareen Riviere
Methods Validation	Acceptable	11/5/2012	Kui Zeng, Michael Trehly
Office of Drug Safety	Acceptable for "Procysbi" as the proprietary name	06/28/2012	Carol Holquist
EA	N/A (categorical exclusion, see page 160 of this review)		
Microbiology	N/A		

## Executive Summary Section

# Chemistry Review for NDA 203389

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA. However, labeling issues are still pending as of the date of this review. Therefore, from the ONDQA perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(6) in its present form until the labeling issues are satisfactorily resolved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

A post-approval commitment made by the applicant via amendments dated December 19, 2012 and February 20, 2013 (see page 120) to include elemental impurities for arsenic, cadmium, lead, and mercury per USP <232> for the drug product specification will be fulfilled by June 5, 2013.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Product

Procysbi (cysteamine bitartrate) delayed-release capsules are available as 25 mg and 75 mg capsules indicated for the management of nephropathic cystinosis in children and adults. The strength of each capsule refers to cysteamine free base content, instead of cysteamine bitartrate (see page 149). The two strengths are (b) (4) and are manufactured from (b) (4) beads with bead size of (b) (4). The enteric-coated (b) (4) beads are encapsulated in size 0 and size 3 blue hard gelatin capsules for the 75 mg and 25 mg strengths, respectively. The dark blue cap is imprinted with 'Raptor' logo in white ink. The light blue body is imprinted with '75 mg' in white ink for the 75 mg capsules and with '25 mg' in white ink for the 25 mg capsules.

The manufacture of cysteamine bitartrate delayed-release capsules involves the following units of operation: (b) (4)

## Executive Summary Section

(b) (4)

No novel excipients are used. The excipients in enteric coated beads are: hypromellose, microcrystalline cellulose, sodium lauryl sulfate, Eudragit L 30 D-55, triethyl citrate, and talc. The capsule shells contain gelatin, titanium dioxide, and FD&C Blue (b) (4).

The proposed specifications (see page 83) for cysteamine bitartrate delayed-release capsules are acceptable. The specifications include appearance, identification (NIR and HPLC), uniformity of dosage units, assay, related substances, water content, dissolution, and microbial limits. The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose. A methods validation request to evaluate the procedure for assay and related substances was sent to Division of Pharmaceutical Analysis (DPA) in St. Louis. In the Method Validation Report Review dated 05-Nov-2012, DPA concludes that the procedure is acceptable for quality control and regulatory purposes. The applicant revised the dissolution analytical procedure and acceptance criterion per Biopharmaceutics Reviewer's recommendation (see page 119), and they are acceptable.

Cysteamine bitartrate delayed-release capsules are packaged in white HDPE (high density polyethylene) bottles. Each bottle includes one oxygen absorber (b) (4) and one (b) (4) desiccant (b) (4).

The 25 mg capsules are packaged as 60 counts in 50 cc bottles. The 75 mg capsules are packaged as 250 counts in 400 cc bottles. Stability data include five registration batches of 25 mg capsules packaged in the to-be-marketed container closure system and a bracket design for 75 mg capsules. Data of nine registration batches of 75 mg capsules were provided: three batches of each packaging configuration as 60 counts in 100 cc bottles, 150 count in 250 cc bottles, and 300 count in 400 cc bottles. The stability data for each strength support the proposed expiration dating period of 18 months when stored at 25°C (77°F), excursions permitted to 15 – 30°C (59 – 86°F).

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(a) is acceptable.

**(2) Drug Substance**

The drug substance is cysteamine bitartrate. Cysteamine bitartrate is manufactured by (b) (4) (b) (4) also supplies cysteamine bitartrate drug substance for the approved product Cystagon. The information on characterization of cysteamine bitartrate, including elucidation of structure and other characteristics, as well as characterization of related substances, the drug substance specification and detailed analytical procedures employed by (b) (4) and the drug substance reference standard is provided in the NDA. All other CMC

## Executive Summary Section

information is referenced to DMF (b) (4) and a letter of authorization has been provided from the DMF holder. The DMF has been reviewed by this reviewer and found to be adequate to support this NDA.

The proposed cysteamine bitartrate specification (see page 30) includes testing for appearance, solubility, color of solution, identification (RP-HPLC, melting range, and IR), cysteamine free base on anhydrous and salt-free basis (RP-HPLC), cysteamine free base "as-is" (w/w% by RP-HPLC), cysteamine free base (%w/w relative to cysteamine free base by RP-HPLC), related substances (RP-HPLC), water, (b) (4) (RP-HPLC), molar ratio of cysteamine free base to (b) (4) residual solvent (b) (4) particle size, (b) (4) and (b) (4). The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose.

A retest date for the drug substance has not been established. Stability study for the drug substance is underway. Until a retest date is established, cysteamine bitartrate is tested by (b) (4) prior to use in the manufacture of cysteamine bitartrate delayed-release capsules. Furthermore, the applicant commits to perform testing of the drug substance by (b) (4) for cysteamine free base, cysteamine, (b) (4) and (b) (4) for every lot of the drug substance to be used for manufacture of the drug product (see page 28).

**B. Description of How the Drug Product Is Intended to Be Used**

Starting dose: 1/4 to 1/6 of the maintenance dose of Procysbi™. The dose should then be raised gradually over four to six weeks to avoid side-effects.

(b) (4)

## Executive Summary Section

Administration Options – Capsules may be swallowed whole or after sprinkling on food or in liquid. The sprinkling mixture must be administered within (b) (4) 30 minutes (b) (4) after preparation (b) (4)

- *Sprinkling on Food:* Open capsules and sprinkle the contents onto approximately 4 ounces (1/2 cup) of applesauce, (b) (4) or berry jelly.
- *Sprinkling in Liquid:* Open capsules and sprinkle the contents into 4 (b) (4) ounces (1/2 cup) of fruit juice (b) (4)

Administration with Food: (b) (4)  
(b) (4) avoid eating for at least 2 hours prior to Procysbi™ dosing and wait at least 30 minutes after Procysbi™ dosing before eating. (b) (4)  
(b) (4) eat only a small amount (~ 4 ounces – ½ cup) of food (b) (4) during the hour before and after Procysbi™ administration.

The assay-dependent therapeutic goal is to maintain a white blood cell (WBC) cystine level < 1 nmol ½ cystine/mg protein, 30 min after dosing.

### C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(6):

Labeling issues are not resolved. In addition, the issue on the established name has not been resolved (see page 149).

## III. Administrative

### A. Reviewer's Signature

See appended electronic signature page

### B. Endorsement Block

See appended electronic signature page

### C. CC Block

Entered electronically in DARRTS

155 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE L CHANG  
03/05/2013

MOO JHONG RHEE  
03/05/2013  
Chief, Branch IV

## FILING CHECKLIST

**NDA Number:**                      **Supplement Number and Type:**      **Established/Proper Name:**

NDA 203-389                              original                                      cysteamine bitartrate

**Applicant:**                              **Letter Date:**                              **Stamp Date:**

Raptor Therapeutics                      4/2/2012                                      4/2/2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		√	Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	√		Also referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?		√	Referenced to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		√	No issues for inclusion in the 74-day letter

*{See appended electronic signature page}*

Marie Kowblansky, Ph.D.  
 CMC Lead  
 Division of Pre-Marketing Assessment #  
 Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of Pre-Marketing Assessment #

Office of New Drug Quality A

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARIE KOWBLANSKY  
05/24/2012

MOO JHONG RHEE  
05/24/2012  
Chief, Branch IV