

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203389Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**ADDENDUM TO PHARMACOLOGY/TOXICOLOGY REVIEW OF NDA 203,389  
DATED March 8, 2013**

**1. Established Pharmacologic Class (EPC)**

The following evaluation of the EPC was provided in the Pharmacology/  
Toxicology review dated March 8, 2013:

**“The Sponsor’s proposed established pharmacologic class for Procysbi (b) (4) is different from the FDA’s established pharmacologic class for cysteamine, which is the following: “cystine depleting agent”. The established pharmacologic class should be the same as the FDA’s version.”**

Cysteamine is an aminothioliol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with cystinosis. Although (b) (4) is listed as the official EPC for cysteamine, this term is not an appropriate choice since it is not clinically meaningful. The review team recommends that the term “cystine depleting agent” be used as the EPC in the Highlights section of the label. We have included Dr. Paul Brown in the team’s discussion of this issue, and have requested that he initiate a process to change the official EPC to “cystine depleting agent”.

Revised Recommendation for Labeling:

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

PROCYSBI™ (cysteamine bitartrate) delayed-release capsules is a cystine depleting agent indicated for the management of nephropathic cystinosis in children and adults. (1.1)

**2. Excipients**

In the Pharmacology/Toxicology review dated March 8, 2013, the maximum daily intake of each excipient was calculated based on daily ingestion of (b) (4) Procysbi capsules containing 75 mg cysteamine free base equivalent (see Comments on Novel Excipients, page 12). Ingestion of (b) (4) capsules per day would be needed to achieve the maximum dose proposed by the Sponsor (b) (4)

Section 2.6 of the labeling (Dose Titration), as recommended by the review team, states the following: **“The dose of PROCYSBI can be increased to a maximum of 1.95 grams/m<sup>2</sup>/day to achieve the target WBC cystine concentration (or plasma cysteamine concentration)”**. Thus, the estimated maximum daily dose of each excipient needs to be changed based on the recommended maximum daily dose of 1.95 g/m<sup>2</sup>/day cysteamine; this higher dose will require the

ingestion of 43 capsules (75 mg strength) in a patient weighing 60 kg (1.62 m<sup>2</sup> body surface area). The revised maximum daily intake of each excipient is summarized in the table below.

**Estimated Maximum Daily Intake of Excipients in Procysbi™ and the Maximum Amounts in FDA-Approved Oral Formulations**

Inactive Ingredients	Amount mg / 25 mg Capsule	Amount mg / 75 mg Capsule	Maximum daily dose (mg) *	Maximum Potency listed in Inactive Ingredient Database for oral administration
Microcrystalline Cellulose (b) (4)	(b) (4)	(b) (4)	(b) (4)	1385.3 mg
Hypromellose	(b) (4)	(b) (4)	(b) (4)	670.04 mg
Sodium lauryl sulfate	(b) (4)	(b) (4)	(b) (4)	51.69 mg
Eudragit L30D-55	(b) (4)	(b) (4)	(b) (4)	140 mg
Triethyl citrate	(b) (4)	(b) (4)	(b) (4)	18.7 mg
Talc	(b) (4)	(b) (4)	(b) (4)	220.40 mg

\*Estimated maximum daily intake of the excipients was calculated based on daily ingestion of 43 capsules containing 75 mg cysteamine free base equivalent (maximum proposed daily dose of 1.95 mg/m<sup>2</sup>/day, approximately 3.2 g/day in an adult with 1.62 m<sup>2</sup> BSA).

The estimated maximum daily intake for hypromellose is lower than the maximum quantity present in the FDA-approved products. However, the estimated maximum daily intake for microcrystalline cellulose (b) (4), Eudragit L30 D-55 (b) (4), sodium lauryl sulfate (b) (4), triethyl citrate (b) (4) and talc (b) (4) is higher than the maximum quantity present in the FDA approved products.

The ADI (acceptable daily intake) for microcrystalline cellulose and talc, as established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), is designated as “not specified”, since these food additives have minimal toxicity (i.e. a numerical ADI is not deemed necessary). The maximum daily intake for triethyl citrate (b) (4) is within the ADI (0-20 mg/kg). Thus, the estimated maximum daily doses of these excipients resulting from Procysbi administration are not considered to be a safety concern.

The estimated maximum daily intake for sodium lauryl sulfate (b) (4) is higher than the maximum quantity listed in the FDA Inactive Ingredient Database. However, the maximum daily dose of sodium lauryl sulfate from an approved oral tablet can be as high as 155 mg (based on the maximum approved dose of the

API), which is (b) (4)-times the estimated maximum daily dose of sodium lauryl sulfate from Procysbi. Therefore, the estimated maximum daily dose of sodium lauryl sulfate from Procysbi administration is not considered to be a safety concern.

The estimated maximum daily intake of Eudragit L30 D-55 (methacrylic acid–ethyl acrylate co-polymer) associated with Procysbi administration is (b) (4). The tolerated dose in rats (600 mg/kg/day) and dogs (80 mg/kg/day) observed in chronic toxicity studies exceeds the maximum human dose by approximately 15-fold and 2-fold, respectively, based on body weight comparison. Comparison of animal and human doses based on mg/kg, rather than mg/m<sup>2</sup>, is justified for Eudragit L30 D-55 based on PK studies in animals that showed no evidence of absorption. Furthermore, it is reasonable to assume that no absorption occurs in humans, based on the high molecular weight (320,000) of methacrylic acid–ethyl acrylate copolymer. Given the absence of any major or dose-limiting toxicity in the chronic studies in rats and dogs, the tolerated doses in these studies provide a reasonable assurance of safety for the maximum daily intake of Eudragit L30 D-55 with Procysbi.

Based on the new maximum daily dose recommended by the review team, the revised estimated maximum daily intake of titanium oxide is (b) (4).

Therefore, the daily intake of titanium oxide from Procysbi will be lower than the maximum amount of titanium oxide in an FDA approved oral drug formulation (1387 mg), as listed in the FDA Inactive Ingredient Database.

Based on the new maximum daily dose recommended by the review team, the revised estimated maximum daily intake of FD&C blue (b) (4) is (b) (4). FD&C blue (b) (4). The maximum daily intake of FD&C blue (b) (4) will be higher than the maximum amount of FD&C blue (b) (4) in an FDA approved oral drug formulation (24.12 mg), as listed in the FDA Inactive Ingredient Database. However, the maximum daily dose of FD&C blue (b) (4) from an approved oral drug product can be as high as 96.48 mg (based on the maximum approved dose of the API), which is (b) (4)-times the estimated maximum daily dose of FD&C blue (b) (4) from Procysbi. Therefore, the estimated maximum daily dose of FD&C blue (b) (4) from Procysbi administration is not considered to be a safety concern.

In conclusion, although the revised recommended maximum daily dose of 1.95 g/m<sup>2</sup>/day cysteamine equivalent (approximately 3.2 g/day in an adult with 1.62 m<sup>2</sup> BSA) results in an increased intake of excipients (approximately 2-fold), the information available from health authorities, U.S. regulations, and toxicity studies still provides a reasonable assurance of safety for the estimated maximum daily intake of each excipient in Procysbi.

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Fang Cai, Ph.D.  
Pharmacologist, DGIEP

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Date

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David B. Joseph, Ph.D.  
Pharmacology Team Leader, DGIEP

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Date

cc:  
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DGIEP  
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/s/  
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FANG CAI  
04/22/2013

DAVID B JOSEPH  
04/22/2013  
I concur.

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 203,389  
Supporting document/s: 1  
Applicant's letter date: March 30, 2012  
CDER stamp date: March 30, 2012  
Product: PROCYSBI™ (Cysteamine Bitartrate Delayed-Release Capsules)  
Indication: Treatment of nephropathic cystinosis  
Applicant: Raptor Therapeutics Inc.  
Novato CA  
Review Division: Division of Gastroenterology and Inborn Errors Products  
Reviewer: Fang Cai, Ph.D.  
Supervisor/Team Leader: David B. Joseph, Ph.D.  
Division Director: Donna Griebel, M.D.  
Project Manager: Jessica Benjamin

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# 1 Executive Summary

## 1.1 Introduction

## 1.2 Brief Discussion of Nonclinical Findings

PROCYSBI™ (cysteamine bitartrate) delayed-release capsules was submitted under a 505(b)(2) New Drug Application. The Sponsor did not conduct nonclinical studies to support clinical testing or submission of a marketing application, nor did the Agency request such studies. Thus, the nonclinical safety assessment was limited to the excipients and impurities in the drug product. The submitted information was sufficient to provide a reasonable assurance of safety for the excipients and impurities.

## 1.3 Recommendations

### 1.3.1 Approvability

From a nonclinical viewpoint, approval of PROCYSBI™ is recommended for treatment of nephropathic cystinosis in children and adults.

### 1.3.2 Additional Non Clinical Recommendations

None

### 1.3.3 Labeling

The labeling should be revised as follows:

#### Established Pharmacologic Class

#### Sponsor's Proposed Version:

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

#### INDICATIONS AND USAGE

PROCYSBI™ (b)(4) is a cystine-depleting (b)(4) indicated for the management of nephropathic cystinosis in children and adults. (1.1)

#### Evaluation:

The Sponsor's proposed established pharmacologic class for Procysbi (b)(4) is different from the FDA's established pharmacologic class for cysteamine, which is the following: "cysteine depleting agent". The established pharmacologic class should be the same as the FDA's version.

**Recommended Version:**

PROCYSBI™ (cysteamine bitartrate) delayed-release capsules is a cysteine depleting agent indicated for the management of nephropathic cystinosis in children and adults. (1.1)

**Sponsor's Proposed Version:**

[Redacted content]

(b) (4)

**Evaluation:**

[Redacted content] (b) (4)  
The rat to human dose ratios were calculated using the recommended maintenance dose for Cystagon [Redacted content] (b) (4)  
However, the proposed maintenance dose for Procysbi [Redacted content] (b) (4)  
Thus, the rat to human dose margins in the proposed labeling is not correct, and should be recalculated using the proposed maintenance dose for Procysbi.

**Recommended Version:**

[Redacted content]

(b) (4)

**Sponsor's Proposed Version:**

[Redacted content]

(b) (4)

[Redacted]

(b) (4)

**Evaluation:**

[Redacted] (b) (4)  
The rat to human dose ratio was calculated using the recommended maintenance dose for Cystagon [Redacted] (b) (4)  
[Redacted] However, (b) (4)  
the proposed maintenance dose for Procysbi [Redacted] (b) (4)  
[Redacted] Thus, the rat to human dose ratio in the proposed labeling is not correct, and should be recalculated using the proposed maintenance dose for Procysbi.

**Recommended Version:**

[Redacted]

(b) (4)

**Sponsor's Proposed Version:**

[Redacted]

(b) (4)

**Evaluation:**

(b) (4)

The rat to human dose ratio was calculated using the recommended maintenance dose for Cystagon (b) (4)

However, the proposed maintenance dose for Procysbi (b) (4)

Thus, the rat to human dose ratio in the proposed labeling is not correct, and should be recalculated using the proposed maintenance dose for Procysbi.

**Recommended Version:**

(b) (4)

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional): 27761-19-9

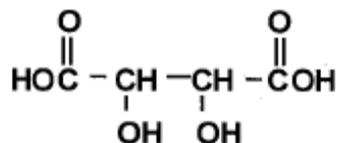
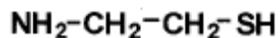
Generic Name: cysteamine bitartrate

Code Name: RP103

Chemical Name: aminothiols,  $\beta$ -mercaptoethylamine (salt)

Molecular Formula/Molecular Weight:  $C_2H_7NS \cdot C_4H_6O_6/227$

Structure:



Pharmacologic Class: cysteine-depleting agent

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 74,146/NDA 20-392 (Mylan Pharmaceuticals, Inc.; CYSTAGON® (cysteamine bitartrate Capsules), and DMF (b) (4), (b) (4), (b) (4)

## 2.3 Drug Formulation

Procysbi™ (cysteamine bitartrate) delayed-release capsules contain 25 or 75 mg of cysteamine free base equivalent, formulated in microspherized (b) (4) beads with enteric coating. The composition of Procysbi™ is summarized in the Sponsor's table below.

**Table 1: Composition of Procysbi™**

Raw Material	Purpose	Grade	Amount (mg) / 75 mg Capsule	Amount (mg)/ 25 mg Capsule
Cysteamine bitartrate	Active ingredient	(b) (4)	221.10 (equivalent to 75 mg of cysteamine free base)	73.70 (equivalent to 25 mg of cysteamine free base)
Microcrystalline Cellulose (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hypromellose (b) (4)				
Sodium lauryl sulfate				
Eudragit L30D-55				
Triethyl citrate				
Talc				
Purified water				
Hard gelatin capsule, size 0 – 75 mg strength				
Hard gelatin capsule, size 3 – 25 mg strength				
White (b) (4)				

The composition of the hard gelatin capsules (sizes 0 and 3) used in the manufacture of Procysbi™ is summarized in the Sponsor’s tables below.

**Table 2: Hard Gelatin Capsule Composition, Size 0**

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

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

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

## 2.4 Comments on Novel Excipients

The excipients used in the (b) (4) beads are (b) (4). Talc is used to (b) (4). The enteric-coating consists of (b) (4).

The excipients present in the sponsor's formulation are all present in oral drug formulations previously approved by the FDA. The table below provides an estimate of the maximum daily intake of each excipient, based on daily ingestion of (b) (4) Procysbi capsules containing 75 mg cysteamine free base equivalent. The maximum amounts of each excipient present in FDA-approved oral formulations is also shown (from FDA Inactive Ingredient Database).

**Table 4: Estimated Maximum Daily Intake of Excipients in Procysbi™ and the Maximum Amounts in FDA-Approved Oral Formulations**

Inactive Ingredients	Amount (mg) / 25 mg Capsule	Amount (mg) / 75 mg Capsule	Maximum daily dose (mg) *	Maximum Potency listed in Inactive Ingredient Database for oral administration
Microcrystalline Cellulose (b) (4)	(b) (4)	(b) (4)	(b) (4)	1385.3 mg
Hypromellose (b) (4)	(b) (4)	(b) (4)	(b) (4)	445 mg
Sodium lauryl sulfate	(b) (4)	(b) (4)	(b) (4)	51.69 mg
Eudragit L30D-55	(b) (4)	(b) (4)	(b) (4)	140 mg
Triethyl citrate	(b) (4)	(b) (4)	(b) (4)	18.7 mg
Talc	(b) (4)	(b) (4)	(b) (4)	220.40 mg

\*Estimated maximum daily intake of the excipients was calculated based on daily ingestion of (b) (4) capsules containing 75 mg cysteamine free base equivalent (b) (4) (b) (4)

The estimated maximum daily intake for three of the excipients is lower than the maximum quantity present in the FDA-approved products. However, the estimated maximum daily intake for Eudragit L30D-55 (b) (4) triethyl citrate (b) (4) and talc (b) (4) is higher than the maximum quantity present in the FDA approved products.

The maximum daily dose of triethyl citrate in patients treated with Procysbi is estimated to be (b) (4). Triethyl citrate has been used in oral pharmaceutical formulations and as a direct food additive. Triethyl citrate is classified as GRAS for use as a direct food substance, with no limitation on its use other than current good manufacturing practice (21 CFR 184.1911). The Joint FAO/WHO Expert Committee on Food Additives designated the ADI (acceptable daily intake) for triethyl citrate as 0-20 mg/kg bodyweight in 1984 and again in 1999. The estimated maximum daily dose (b) (4) falls within the ADI range. Therefore, the estimated maximum daily dose of triethyl citrate resulting from Procysbi administration is not considered to be a safety concern.

The maximum daily dose of talc in patients treated with Procysbi is estimated to be (b) (4). Talc has been widely used as a food additive or as an anticaking agent, coating agent, or texturing agent in pharmaceutical products. It is classified as GRAS for use as a direct food ingredient (21 CFR 170.30). Talc is also classified as a color additive for drugs (21 CFR 73.1550). The FDA Select Committee on GRAS Substances (SCOGS) reviewed the available information on talc and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when talc is used at the currently accepted levels, or at levels that might reasonably be expected in the future.

Furthermore, in 1986, the Joint FAO/WHO Expert Committee on Food Additives designated the ADI for talc as “not specified”. Therefore, the estimated maximum daily dose of talc (b) (4) resulting from Procysbi administration is not considered to be a safety concern.

### **Methacrylic acid–ethyl acrylate co-polymer (Eudragit L30D-55):**

In a 6-month oral toxicity study, rats (30/sex/group) were treated with Eudragit L30D-55 at 0, 200, 600, and 1500 mg/kg/day by stomach tube (b) (4). The following parameters were examined: clinical signs of toxicity, mortality, body weight, food consumption, ophthalmology, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, and histopathology. Eudragit L30D-55 reduced body weight gain (17-19%) at 1500 mg/kg/day and induced inflammation in the intestine at 600 and 1500 mg/kg/day (1/60 and 2/60 rats, respectively). The tolerated dose was 600 mg/kg/day.

In a 1-year oral toxicity study, Eudragit L30D-55 was given to dogs by oral capsules at 0, 20, 40, and 80 mg/kg/day (b) (4). No treatment-related changes in any treatment group were observed. The high dose of 80 mg/kg/day is considered as the tolerated dose.

The estimated maximum daily intake of Eudragit L30D-55 associated with Procysbi administration is (b) (4). Given the absence of any major or dose-limiting toxicity in the chronic studies in rats and dogs, the tolerated doses in these studies provide a reasonable assurance of safety for the maximum daily intake of Eudragit L30D-55 with Procysbi. The tolerated doses in rats (600 mg/kg/day) and dogs (80 mg/kg/day) exceeded the maximum human dose by approximately 5-fold and 2-fold, respectively, based on a body surface area comparison.

### **Gelatin Capsule Ingredients:**

The excipients present in the hard gelatin capsule are all present in oral drug products previously approved by the FDA. Titanium oxide is a food color additive, and may be safely used for coloring food in general. However, the quantity of titanium dioxide should not exceed 1 percent food weight (21 CFR 73.575). The maximum amount of titanium oxide in an FDA approved oral drug formulation is 1387 mg. The content of titanium oxide in each capsule size for Procysbi is (b) (4). Since the empty capsule weight was not provided, it is not possible to calculate the maximum daily intake of titanium oxide. However, it should be noted that the weight of size 0 gelatin capsules available from commercial vendors is stated to be in the range of (b) (4). Therefore, it is very likely that the daily intake of titanium oxide will be lower than 1387 mg (FDA Inactive Ingredient Database) in patients treated with Procysbi, even at the maximum proposed dose (i.e. (b) (4) capsules, 75 mg strength).

FD&C blue (b) (4) is a color additive contained in the hard gelatin capsule, and may be safely used for coloring ingested drugs in amounts consistent with current good manufacturing practice (21 CFR 74.1102). The maximum amount of FD&C blue (b) (4) in

an approved oral drug formulation is 24.12 mg. The content of FD&C blue (b) (4) in each capsule size for Procysbi is (b) (4). Since the Sponsor did not provide the empty capsule weight, it is not possible to calculate the maximum daily intake of FD&C blue (b) (4) in patients treated with Procysbi. However, based on the weight of size 0 gelatin capsules available from commercial vendors, it is very likely that the maximum daily intake will be lower than 24.12 mg (FDA Inactive Ingredient Database).

## 2.5 Comments on Impurities/Degradants of Concern

The table below shows the proposed acceptance criteria (limits) for impurities in the drug product. The proposed limits for several impurities (highlighted in the table) exceed the ICH qualification threshold of 0.2% (ICH guidance Q3B(R2)). The table also shows the range of impurity levels in five lots of the Sponsor's drug product.

**Table 5: Proposed acceptance criteria of related substances for cysteamine bitartrate drug product (10/9/2012 amendment)**



(b) (4)

Table 5 (above) shows that there are eight impurities with proposed acceptance criteria that exceed the ICH limit (0.2%). The most abundant of these impurities is (b) (4) which is the (b) (4) (b) (4). The structure of six of these impurities is shown in the table below.

**Table 6: Chemical structures of impurities with proposed limits in excess of the ICH qualification threshold**

(b) (4)



It is reasonable to assume that all of the impurities shown in table 6 are degradants of the drug substance, based on the structures. For these impurities, the acceptance criteria for stability exceeds the acceptance criteria for release (see table 5), with one exception. This approach indicates that the Sponsor considers these impurities to be degradants that may accumulate during storage. The accumulation of drug substance degradants in Procysbi and the reference product, Cystagon, is not expected to be substantially different. Therefore, the proposed impurity limits that exceed the ICH qualification threshold are acceptable. It is noted that one unidentified impurity, (b) (4) has an acceptance criteria for stability (b) (4) that exceeds the ICH qualification threshold (0.2%). However, it is likely that (b) (4) is also a degradant of the drug substance, given that the acceptance criteria for release is lower (b) (4). It is important to note that the drug substance in Procysbi and Cystagon are

supplied by the same manufacturer, under the same DMF. Thus, the potential for toxicity due to impurities (either process impurities or degradants of the drug substance) is assumed to be very similar in Procysbi and Cystagon.

## 2.6 Proposed Clinical Population and Dosing Regimen

Procysbi (cysteamine bitartrate) delayed-release capsules is indicated for the treatment of nephropathic cystinosis in children and adults. The dose regimen includes starting and maintenance doses. The starting dose will be 1/4 to 1/6 of the maintenance dose of cysteamine. The dose should then be raised gradually over 4 to 6 weeks to avoid side-effects. (b) (4)

The dose levels are expressed as cysteamine free base equivalent.

## 2.7 Regulatory Background

Procysbi was developed under IND 103,694, submitted on April 17, 2009. The active ingredient, cysteamine bitartrate, is contained in the approved drug product, Cystagon.

## 3 Studies Submitted

### 3.1 Studies Reviewed

- 1). A 6-month oral toxicity study with Eudragit L 30D-55 in rats
- 2). A 1-year oral toxicity study with Eudragit L 30D-55 in dogs

The studies were reviewed under "Comments on Novel Excipients".

### 3.2 Studies Not Reviewed

None.

### 3.3 Previous Reviews Referenced

None.

## 4 Pharmacology

Not applicable.

## 5 Pharmacokinetics/ADME/Toxicokinetics

Not applicable.

## **6 General Toxicology**

### **6.1 Single-Dose Toxicity**

Not applicable.

### **6.2 Repeat-Dose Toxicity**

Not applicable.

## **7 Genetic Toxicology**

Not applicable.

## **8 Carcinogenicity**

Not applicable.

## **9 Reproductive and Developmental Toxicology**

Not applicable.

## **10 Special Toxicology Studies**

Not applicable.

## **11 Integrated Summary and Safety Evaluation**

Procysbi™ (cysteamine bitartrate) delayed-release capsules was developed as a treatment for nephropathic cystinosis, a rare lysosomal storage disease primarily affecting children. Cysteamine bitartrate is a cysteine depleting agent, which lowers the cystine content of cells in patients with cystinosis. This drug is currently marketed under the trade name Cystagon® for the treatment of nephropathic cystinosis in children and adults, and is available for oral administration as 50 mg or 150 mg capsules with a recommended dosing interval of every 6 hours. This dosing schedule requires patients to be awakened in the middle of the night to take their medication in order to maintain adequate white blood cell cystine levels. However, the Sponsor's formulation (delayed-release capsules) will allow the dosing interval to be increased from Q6H to Q12H. Thus it will be easier for patients to comply with the dosing schedule for Procysbi, with an expected improvement in quality of life.

This NDA was submitted under section 505(b)(2). The reference drug is Cystagon (cysteamine bitartrate) Capsules (NDA 20,392). The Sponsor did not conduct nonclinical studies to support clinical testing or submission of a marketing application, nor did the Agency request such studies. The sponsor submitted a letter of authorization from (b) (4) to allow FDA access to DMF (b) (4) which contains toxicity studies of the excipient Eudragit® L30D-55.

All of the inactive ingredients in Procysbi are listed in the FDA Inactive Ingredient Database. Based on the proposed maximum daily dose of (b) (4) a patient will consume a total of (b) (4) capsules per day (75 mg strength). Therefore, the total amounts of the following inactive ingredients in (b) (4) capsules would exceed the listed maximum level per oral tablet or capsule in the FDA Inactive Ingredient Database (this database does not provide the number of tablets or capsules ingested daily at the approved dose): triethyl citrate, talc, and methacrylic acid-ethyl acrylate co-polymer (Eudragit L30D-55).

Triethyl citrate is considered as GRAS under 21 CFR184.1911. An acceptable daily intake (ADI) of up to 20 mg/kg was established for triethyl citrate by the Joint FAO/WHO Expert Committee on Food Additives. The ADI exceeds the estimated maximum daily intake of (b) (4) for triethyl citrate. Therefore, the estimated maximum daily dose of triethyl citrate resulting from Procysbi administration is not considered to be a safety concern.

Talc is a finely powdered mineral composed of hydrated magnesium silicate [H<sub>2</sub>Mg<sub>3</sub>(SiO<sub>4</sub>)<sub>4</sub>], and is widely used as a food additive and texturing agent in pharmaceutical products. It is classified as GRAS for use as a direct food ingredient (21 CFR, 170.30). Talc is also classified as a color additive for drugs (21 CFR 73.1550). The FDA Select Committee on GRAS Substances (SCOGS) reviewed the available information on talc and concluded that there is no evidence that demonstrates or suggests reasonable grounds to suspect a hazard to the public when talc is used at the currently accepted levels, or at levels that might reasonably be expected in the future. In 1986, the Joint FAO/WHO Expert Committee on Food Additives designated the ADI as "not specified". Based on the regulatory information and the recommended ADI, the estimated maximum daily dose of talc (b) (4) in patients treated with Procysbi is not considered to be a safety concern.

The estimated maximum daily intake of Eudragit L30D-55 associated with Procysbi administration is (b) (4). In chronic toxicity studies, Eudragit L30D-55 was well tolerated at oral doses up to 600 mg/kg/day in rats and 80 mg/kg/day in dogs. The tolerated doses in rats (600 mg/kg/day) and dogs (80 mg/kg/day) exceeded the maximum human dose by approximately 5-fold and 2-fold, respectively, based on a body surface area (mg/m<sup>2</sup>) comparison. Given the absence of any major or dose limiting toxicity in the chronic toxicity studies, the safety margins derived from these studies (5 in rats, 2 in dogs) provide a reasonable assurance of safety for the maximum daily intake of Eudragit L30D-55.

Titanium oxide is food color additive contained in the hard gelatin capsule used for Procysbi. This excipient may be safely used for coloring food in general. However, the quantity of titanium dioxide should not exceed 1 percent food weight (21 CFR 73.575). The maximum amount of titanium oxide in an FDA approved oral drug formulation is 1387 mg. The content of titanium oxide in each capsule size for Procysbi is (b) (4). Since the empty capsule weight was not provided, it is not possible to calculate the maximum daily intake of titanium oxide. However, it should be noted that the weight of size 0 gelatin capsules available from commercial vendors is stated to be in the range of (b) (4). Therefore, it is very likely that the daily intake of titanium oxide will be lower than 1387 mg (FDA Inactive Ingredient Database) in patients treated with Procysbi, even at the maximum proposed dose (i.e. (b) (4) capsules, 75 mg strength).

FD&C blue (b) (4) is a color additive contained in the hard gelatin capsule, and may be safely used for coloring ingested drugs in amounts consistent with current good manufacturing practice (21 CFR 74.1102). The maximum amount of FD&C blue (b) (4) in an approved oral drug formulation is 24.12 mg. The content of FD&C blue (b) (4) in each capsule size for Procysbi is (b) (4). Since the Sponsor did not provide the empty capsule weight, it is not possible to calculate the maximum daily intake of FD&C blue (b) (4) in patients treated with Procysbi. However, based on the weight of size 0 gelatin capsules available from commercial vendors, it is very likely that the maximum daily intake will be lower than 24.12 mg (FDA Inactive Ingredient Database).

The specifications for Procysbi™ include limits for individual impurities that exceed the ICH qualification threshold. However, all of these impurities appear to be degradants of the drug substance. The accumulation of drug substance degradants in Procysbi™ and in the reference product, Cystagon, is not expected to be substantially different. Therefore, the proposed impurity limits that exceed the ICH qualification threshold are acceptable.

In conclusion, the information available from health authorities, U.S. regulations, and toxicity studies provide a reasonable assurance of safety for the estimated maximum daily intake of the excipients in Procysbi. Therefore, from a nonclinical standpoint, this NDA should be approved.

## 12 Appendix/Attachments

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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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FANG CAI  
03/08/2013

DAVID B JOSEPH  
03/08/2013

I concur with Dr. Cai's recommendations. The Maternal Health reviewer will recommend revisions in the Pregnancy and Nursing Mothers sections of the labeling.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

**NDA/BLA Number: 203,389    Applicant: Raptor**

**Stamp Date: 3/30/2012**

**Drug Name: RP103**

**NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			NA: No studies were required or requested.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			NA
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			NA
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		√	
11	Has the applicant addressed any abuse potential issues in the submission?		√	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_Yes\_\_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Fang Cai

5/6/2012

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Reviewing Pharmacologist

Date

David Joseph

5/9/2012

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Team Leader/Supervisor

Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

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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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FANG CAI  
05/09/2012

DAVID B JOSEPH  
05/09/2012