CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213491Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: This NDA is recommended for **Approval** from the OPQ perspective.

NDA 213491
Review #1

Drug Name/Dosage Form	Procysbi (cysteamine bitartrate) delayed-release oral granules
Strength	75 mg per sachet OR 300 mg per sachet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Horizon Pharma USA, Inc.; Lake Forest, IL
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	May 16, 2019	OPQ
Amendment, Labeling	July 9, 2019	ONDP
Amendment, Labeling	July 12, 2019	ONDP
Amendment	Aug 2, 2019	ONDP
Amendment	Oct 9, 2019	OPF
Amendment, Labeling	Oct 29, 2019	ONDP
Amendment	Nov 1, 2019	OPF
Amendment, labeling	Nov 12, 2019	ONDP
Amendment	Nov 13, 2019	ONDP

Quality Review Team

Discipline	Reviewer	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product and Environmental Analysis (EA)	Ryan Holland	Moo-Jhong Rhee
Process, Facilities and Microbiology	Kejun Cheng	Yaodong (Tony) Huang
Biopharmaceutics	Vincent Li	Tapash Ghosh
Microbiology	Nutan Mytle	Neal Sweeney
Regulatory Business Process Manager	Oumou Barry	N/A
Application Technical Lead	Hitesh Shroff	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		Active	N/A	LOA January 29, 2019

N/A: There is enough data in the application, therefore, the DMF did not need to be reviewed.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	203389	Procysbi delayed-release capsules (approved in 2013) for CMC information relevant to drug substance and drug product

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg or 300 mg/packet.

The Office of Process and Facilities (OPF) has made a final overall "**Approval**" recommendation for the facilities involved in this application,

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is acceptable from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for "**Approval"**.

II. Summary of Quality Assessments

A. Product Overview

Procysbi is a cystine-depleting agent that lowers the cystine content of cells in patients with nephropathic cystinosis, an inherited defect of lysosomal transport.

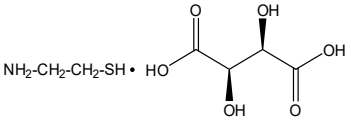
The proposed drug product, Procysbi packet, contains 75 mg or 300 mg cysteamine as delayed-release granules. The proposed drug product is formulated as a higher strength drug product than previously approved Procysbi delayed-release capsules, 25 mg or 75 mg. The delayed-released granules are the same in both capsules and packets dosage forms.

<table>
<tr><td>Proposed Indication(s) including Intended Patient Population</td><td>For the treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older</td></tr>
<tr><td>Duration of Treatment</td><td>As long as needed</td></tr>
<tr><td>Maximum Daily Dose</td><td>
<table>
<tr><th rowspan="2">Weight in kilograms</th><th colspan="2">Starting PROCYSBI Dosage in mg every 12 hours, as a Fraction of the Maintenance Dosage</th><th rowspan="2">Maintenance PROCYSBI Dosage in mg every 12 hours*</th></tr>
<tr><th>1/6 of dosage</th><th>1/4 of dosage</th></tr>
<tr><td>5 or less</td><td>25</td><td>50</td><td>200</td></tr>
<tr><td>6 to 10</td><td>50</td><td>75</td><td>300</td></tr>
<tr><td>11 to 15</td><td>75</td><td>100</td><td>400</td></tr>
<tr><td>16 to 20</td><td>100</td><td>125</td><td>500</td></tr>
<tr><td>21 to 25</td><td>100</td><td>150</td><td>600</td></tr>
<tr><td>26 to 30</td><td>125</td><td>175</td><td>700</td></tr>
<tr><td>31 to 40</td><td>125</td><td>200</td><td>800</td></tr>
<tr><td>41 to 50</td><td>150</td><td>225</td><td>900</td></tr>
<tr><td>51 kg and greater</td><td>175</td><td>250</td><td>1000</td></tr>
</table>
</td></tr>
<tr><td>Alternative Methods of Administration</td><td>N/A</td></tr>
</table>

B. Quality Assessment Overview

Drug Substance:

Cysteamine bitartrate is the active ingredient in Procysbi delayed release oral granules. It is a white powder that is freely soluble in water. It is a chiral molecule. (b) (4) It is a tartaric acid salt of cysteamine. The chemical name for cysteamine bitartrate is ethanethiol, 2-amino, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt). Its molecular weight is 227.24 and the molecular formula is $C_2H_7NS \bullet C_4H_6O_6$. It has the following chemical structure:



Cysteamine bitartrate is manufactured by (b) (4)
The detailed drug substance CMC information including synthetic scheme, control of raw materials, control of critical steps and intermediate; process validation studies, manufacturing process and development; characterization, impurities/degradant characterization, specification, the analytical procedures, reference standard, container closure system, and stability data is provided in the cross-referenced NDA 203389.

The overall quality of cysteamine bitartrate is assured by its specification which includes appearance, identity by IR and HPLC; assay by HPLC, related substances by HPLC, tartrate counter ion content by HPLC, water content and particle size. All potential impurities are controlled per ICH Q3A. The non-compendial in-house analytical methods were validated.

The drug substance is packed in (b) (4)

The CMC information was reviewed by the drug substance reviewer, Dr. Friedrich Burnett, and concluded that the submitted information is adequate to support the drug product (see the **Drug Substance** review).

Drug Product:

Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg or 300 mg/packet. Cysteamine bitartrate (b) (4) achieve delayed-release properties. The drug product is supplied as packets to administer the contents via gastronomy tube or mix with food or liquid. The inactive ingredients in the drug product are the following: microcrystalline cellulose, hypromellose, sodium lauryl sulfate, Eudragit L30D-55, triethyl citrate, talc and water. (b) (4) All ingredients are compendial.

The overall control strategy for the drug product is deemed adequate based on raw material controls and drug product specification including appearance, identity by HPLC and NIR, strength by drug substance assay, impurities by HPLC, uniformity of dosage units per USP <905> and dissolution per USP <711> in 0.1N HCl and at pH 6.8 to confirm delayed-release characteristics of the drug product. The applicant has provided a risk assessment statement from (b) (4)

The drug product is tested for Microbial Limits at release using a validated method consistent with USP <61> and USP <62>. The Microbial Limits specification for the drug product complies with USP <1111> and is acceptable from a Product Quality Microbiology perspective. (see **Microbiology** review)

The granules from the single-use packet can be sprinkled on applesauce, berry jelly or fruit juice (except grapefruit juice) and the mixture (food/drug combination) should be swallowed within 30 minutes of preparation.

The drug product packets are (b) (4)
placed in cartons at either a 60 count or 120 count for both the 75 mg and 300 mg dosage strengths.

Based on satisfactory 12-month long-term stability at 5°C and 6-month accelerated stability at 25°C from three primary registration batches of the drug product (2 batches of 75 mg strength, 1 batch of 300 mg strength) assuring its identity, strength, purity, and quality, the proposed **24-month of expiration dating period** is granted when stored at 5°C in the proposed container closure system per drug product reviewer, Dr. Ryan Holland (see the **Drug Product** review).

Manufacturing:
The drug product, Procysbi delayed-release oral granules, is manufactured by (b) (4)

(b) (4)
The drug product manufacturing process was reviewed by Dr. Kejun Cheng and was found to be acceptable (see the **Manufacturing Integrated Assessment** review).

The overall control strategy for the drug product is deemed adequate based on raw material controls and specification.

The drug substance, cysteamine bitartrate, manufactured at (b) (4) conforms to the requirements (specification) for drug product formulation of Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg and 300 mg.

Facilities:
The Office of Process and Facilities (OPF) reviewer, Dr. Kejun Cheng has made an "Adequate" recommendation for the drug substance manufacturing and testing facilities and also has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (see the **Manufacturing Integrated Assessment** review).

Environmental Assessment: The applicant's claim of categorical exclusion under 21 CFR Part 25.31(a) from the preparation of an Environmental Analysis or an Environmental Impact Statement for Procysbi delayed-release oral granules, 75 mg and 300 mg is deemed acceptable. (see **Drug Product** Review)

Biopharmaceutics: The drug product (75mg and 300mg/packet) dissolution method is the same as the one used in NDA 203389 for Procysbi delayed-release capsules for 25mg and 75mg. However, for 300 mg packets, the rotation speed was increased (b) (4) The drug product dissolution method development, dissolution method, dissolution data and dissolution specification are deemed adequate from Biopharmaceutics perspective. (see the **Biopharmaceutics** review)

Labeling: The proposed labels and labeling are deemed adequate from the CMC perspective. (see **Labels/ Labeling** review).

C. Lifecycle Management Consideration: None

D. Special Product Quality Labeling Recommendations: None

E. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
November 25, 2019

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
PROCYSBI® (cysteamine bitartrate) delayed-release oral granules

Initial U.S. Approval: 1994

Item	Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	PROCYSBI	**Adequate**:
Established name(s)	Cysteamine bitartrate delayed-release capsules Cysteamine bitartrate delayed-release oral granules	**Adequate**: Capsules: Adequate (see the gray assessment of PI box on page 10 for discussion on established name). It is the same as in the PROCYSBI label approved under NDA 203389 Granule sachets: Adequate (see the gray assessment of PI box on page 10 for discussion on established name). The new dosage form is appropriately stated.
Route(s) of administration	Oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Delayed-release capsules: 25 mg and 75 mg cysteamine Delayed-release oral granules: 75 mg and 300 mg cysteamine	**Adequate**: Both dosage forms and strengths are clearly stated.
Assess if the tablet is scored. And if product meets guidelines	n/a	
For injectable drug products for parental administration, use appropriate package type	n/a	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

- ❖ Dose finding, dosing instructions, and medical monitoring subsections are identical to the PROCYSBI label approved under NDA 203389.
- ❖ The administration subsection's general caution statements, proposed in NDA 213491, match the PROCYSBI label approved under NDA 203389.
- ❖ The information below has been slightly altered from the original labeling info, to include the sachets (packets) as a source of delayed release granules.

Follow the instructions below for administration of the contents from capsule(s) or packet(s) with food or liquid. *Administration of PROCYSBI with foods and liquids not included below has not been studied clinically and is not recommended.*

Administration with Applesauce or Berry Jelly:

1. Place approximately 4 ounces (1/2 cup) or a smaller amount that can be consumed in one feeding of either applesauce or berry jelly into a clean container.
2. Open the capsule(s) or packet(s).
3. Sprinkle all the intact granules that are inside the capsule(s) or packets(s) on applesauce or berry jelly.
4. Mix the granules with the applesauce or berry jelly. Do not crush the granules.
5. Consume the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce or berry jelly and granules for later use.

Administration with Fruit Juice (except grapefruit juice):

1. Pour approximately 4 ounces (1/2 cup) of fruit juice into a clean cup.
2. Open the capsule(s) or packet(s).
3. Sprinkle all the intact granules into the juice.
4. Gently stir until mixed. Do not crush the granules.
5. Drink the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the fruit juice and granules mixture for later use.

Administration with Applesauce via a Gastrostomy (G) Tube (14 French or larger)

A bolus (straight) feeding tube is recommended.

1. Flush the gastrostomy tube button first with 5 mL of water to clear the button.
2. Open the capsule(s) or packet(s) and empty the granules into a clean container with approximately 4 ounces (1/2 cup) of applesauce (b) (4) Use only strained applesauce with no chunks. A minimum of 1 ounce (1/8 cup) of applesauce may be used (b) (4) children 25 kg or less starting PROCYSBI at a dose of 1 or 2 capsule(s) or packet(s).
3. Mix the intact granules into the applesauce Do not crush the granules.
4. Draw up the mixture into a syringe. Keep the feeding tube horizontal during administration and apply rapid and steady pressure (10 mL/10 seconds) to dispense the syringe contents into the tube within 30 minutes of preparation.
5. Repeat step 3 until all of the mixture is administered. Do not save the applesauce and granule mixture for later use.
6. Draw up a minimum of 10 mL of fruit juice or water into another syringe, swirl gently, and flush the tube.

Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See the instructions above for the preparation of granule/food/drink mixtures, to be taken orally of via gastrostomy tube.	**Adequate:** Dose finding, dosing instructions, medical monitoring, and the administration subsection's general caution statements, proposed in NDA 213491, match the PROCYSBI label approved under NDA 203389.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

PROCYSBI delayed-release capsules:

- 25 mg cysteamine: the capsules have a light blue opaque cap imprinted with "PRO" in white ink and a light blue opaque body imprinted with "25 mg" in white ink.
- 75 mg cysteamine: the capsules have a dark blue opaque cap imprinted with "PRO" in white ink and a light blue opaque body imprinted with "75 mg" in white ink.

PROCYSBI delayed-release oral granules:

- 75 mg cysteamine: white to off-white granules packed in (b) (4) packet
- 300 mg cysteamine: white to off-white granules packed in (b) (4) packet

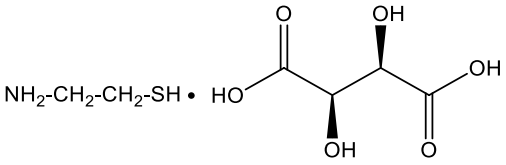
Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Capsules and oral granules	**Adequate**: both dosage forms are distinguished.
Strength(s) in metric system	Each PROCYSBI capsule contains either 25 mg or 75 mg of cysteamine free base. Each PROCYSBI sachet contains either 75 mg or 300 mg of cysteamine free base	**Adequate**: The strengths of the capsules and sachets are based on cysteamine free base, consistent with current salt policy. The amounts of cysteamine bitartrate added to produce the listed strengths are included in the description section (11) of the PI
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	The API is a bitartrate salt of cysteamine.	**Adequate**: Based on historical exception rules in the "Salt Drug Substance Guidance"

A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The capsules have a light blue opaque cap imprinted with "PRO" in white ink and a light blue opaque body imprinted with either "25 mg" or "75 mg" in white ink. The sachets or packets appear as (b) (4) containing white to off-white granules.	**Adequate**: The capsule description matches that of the PROCYSBI label approved under NDA 203389. The granule description is consistent with the DP specifications and with the description of the granules loaded into the capsules
Assess if the tablet is scored. And if product meets guidelines	n/a	Drug product is not a tablet
Injectable drug products for parental administration, use appropriate package type	n/a	Drug product is not an injectable dosage form

1.2.3 Section 11 (DESCRIPTION)

PROCYSBI, for oral administration, is a cystine-depleting agent that 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, (2*R*,3*R*)-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 $C_2H_7NS \bullet C_4H_6O_6$. It has the following chemical structure:



Each PROCYSBI delayed-release capsule contains either 25 mg cysteamine (equivalent to 74 mg cysteamine bitartrate) or 75 mg cysteamine (equivalent to 221 mg cysteamine bitartrate).

Each packet of PROCYSBI delayed-release oral granules contains either 75 mg (equivalent to 221 mg cysteamine bitartrate) or 300 mg cysteamine (equivalent to 884 mg cysteamine bitartrate).

PROCYSBI delayed release granules contain the following inactive ingredients: Eudragit® L 30 D-55, hypromellose, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc, and triethyl citrate. Capsule shell ingredients are gelatin, ink (blue and white), and titanium dioxide.

Item	Information Provided in the NDA	Assessor's Comments

Proprietary and established name(s)	PROCYSBI; *No established name*	**Adequate**: The proper establish name is not included; despite the inclusion of all required pieces of the establish name throughout the description. However, the establish name is not explicitly stated in the Description section of the PROCYSBI labeling approved under NDA 203389. The approved NDA serves as precedent for the acceptance of the Description section for the proposed labeling in NDA 213492
Dosage form(s) and route(s) of administration	The capsules and sachets (packets) both contain the same delayed-release granules. Both dosage forms are intended for oral administration.	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	The active ingredient is described as a bitartrate salt of cysteamine.	**Adequate**: The strengths of the capsules and sachets are based on cysteamine free base consistent with current salt policy with correct equivalency statements.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Hypromellose, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc, and triethyl citrate, and Eudragit® L 30 D-55	**Adequate**: All excipients are compendial. All are listed by the proper USP titles, except Eudragit® (USP: Methacrylic acid and ethyl acrylate copolymer dispersion). However, Eudragit®, was accepted for inclusion in the PROCYSBI label approved under NDA 203389
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust pH or make isotonic, include the name and statement of effect.	n/a	Drug product is not an injectable dosage form
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	Drug product does not contain alcohol
Statement of being sterile (if applicable)	n/a	Drug product is not intended to be a sterile product
Pharmacological/ therapeutic class	Cystine-depleting agent that lowers the cystine content of cells in patients with nephropathic cystinosis	**Adequate**
Chemical name, structural formula, molecular weight	ethanethiol, 2-amino, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt)	**Adequate**: Chemical name, and molecular weight/ formula are provided with correct molecular structure.

	Molecular Formula: $C_2H_7NS \bullet C_4H_6O_6$ Molecular Weight: 227.24	
If radioactive, statement of important nuclear characteristics.	n/a	Drug product is not radioactive
Other important chemical or physical properties (such as pKa or pH)	n/a	n/a
For oral prescription drug products, include gluten statement if applicable	n/a	Drug product is not an oral dosage form
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	**Adequate**: All information is accurate and necessary to describe the product. No marketing promotional terms are included

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

How Supplied

PROCYSBI (cysteamine bitartrate) delayed-release capsules

- **25 mg cysteamine**: A hard gelatin capsule with light blue opaque cap imprinted with "PRO" in white ink and light blue opaque body imprinted with "25 mg" in white ink, supplied as bottle of 60 capsules (NDC 75987-100-04). Each bottle contains one desiccant canister and one oxygen absorber canister.
- **75 mg cysteamine**: A hard gelatin capsule with dark blue opaque cap imprinted with "PRO" in white ink and light blue opaque body imprinted with "75 mg" in white ink, supplied as bottle of 250 capsules (NDC 75987-101-08). Each bottle contains one desiccant canister and two oxygen absorber canisters.

PROCYSBI (cysteamine bitartrate) delayed-release oral granules

- **75 mg cysteamine:** (b) (4) containing white to off-white granules, supplied as 60 packets in a carton (NDC 75987-(b) (4)-13).
- **75 mg cysteamine:** (b) (4) containing white to off-white granules, supplied as 120 packets in a carton (NDC 75987-(b) (4)-14).
- **300 mg cysteamine:** (b) (4) containing white to off-white granules, supplied as 60 packets in a carton (NDC 75987-(b) (4)-13).
- **300 mg cysteamine:** (b) (4) containing white to off-white granules, supplied as 120 packets in a carton (NDC 75987-(b) (4)-14).

(b) (4)

- Dispense (b) (4) in original packaging. Do not subdivide or repackage.

Storage and Handling

- [redacted] (b) (4)
- [redacted] (b) (4)
- Protect from light and moisture.
- Do not remove desiccant or oxygen absorber(s) from the bottle . Keep bottles tightly closed in a dry place.
- [redacted] (b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Delayed-release capsules and Delayed-release oral granules	**Adequate:** Both available dosage forms are included in PI section 16
Strength(s) in metric system	25 mg and 75 mg cysteamine in capsule form 75 mg and 300 mg cysteamine in sachets of oral granules	**Adequate**: The strength of the capsules and sachets are based on cysteamine free base, consistent with current salt policy.
Available units (e.g., bottles of 100 tablets)	Capsules: 60 caps/bottle for 25 mg and 250 caps/bottle for 75 mg Granule packets: 60 packets/ carton for 75 mg and 300 mg	**Adequate**: All dosage forms, strengths and packaging sizes are accurately listed.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsules: Hard gelatin capsule with light blue opaque cap imprinted with "PRO" in white ink and light blue opaque body imprinted with either "25 mg" or "75 mg" in white ink. (NDC 75987-100-04 for 25 mg and NDC 75987-101-08 for 75 mg) Granule packets: Packets contain white to off-white granules; 75 mg supplied as 60 packets / carton (NDC 75987-(b) (4)-13), 75 mg supplied as 60 packets / carton (NDC 75987-(b) (4)-14), 300 mg supplied as 60 packets / carton (NDC 75987-(b) (4)-13), 300 mg supplied as 60 packets / carton (NDC 75987-(b) (4)-14)	**Adequate**: physical; descriptions of all dosage forms, strengths and packaging sizes are accurately listed. Unique NDC numbers are provided for each.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	Drug product is not a tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-	n/a	Drug product is not an injectable dosage form

dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) • Dispense (b) (4) in original packaging. Do not subdivide or repackage. (b) (4) • Protect from light and moisture. • (b) (4) Do not remove desiccant or oxygen absorber(s) from the bottle . Keep bottles tightly closed in a dry place. • (b) (4) Do not store PROCYSBI oral granules in opened packets.	**Adequate**: Special handling concerns for both dosage forms are clearly stated.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	Each bottle of capsules contains one desiccant canister and one oxygen absorber canister	**Adequate**: Desiccant and oxygen absorber are only included in the capsule CCS. The capsule dosage form was approved in 04/2013.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature, 20°C to 25°C (68°F to 77°F).	**Adequate**: Standard numerical storage conditions are clearly stated.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	n/a	
Include information about child-resistant packaging	n/a	The Patient Information sheet states, “Keep PROCYSBI and all medicines out of the reach of children.

1.2.5 Other Sections of Labeling

Much of the administration information in section 2 is also included in section 17 (PATIENT COUNSELING INFORMATION). Adequate

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	**Distributed by:** Horizon Pharma USA, Inc. Lake Forest, IL 60045	**Adequate**: Manufacturers information is up to date.

Assessment of the full Prescribing Information: *{Adequate}*

Justification for including the salt form in the established name:
The strengths of the drug product refer to cysteamine free base, instead of cysteamine bitartrate. The USP Salt Policy stipulates that the USP will use the name of the active moiety, instead of the name of the salt, when creating drug product monograph titles, and that the strength should also be expressed in terms of the active moiety rather than salt equivalent. Therefore, based on the USP Salt Policy, "cysteamine" is to be used as the established name.

However, exceptions to this USP Salt Policy are taken with justification (for safety or historical reasons) that, adopting the salt policy for the established name of this application could potentially confuse healthcare providers as well as patients who have been taking Cystagon (cysteamine bitartrate) capsules or also previously approved Procysbi (cysteamine bitartrate) capsules. Since both Cystagon and Procysbi adopted cysteamine bitartrate in their established names with their strengths based on cysteamine free base, the established name for Procysbi oral granules in this application will retain the salt form in the established name with the strength based on the free base.to be in line with the products available on the market.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): *{Adequate}*
Medication guide and instruction for use inserts are also provided as part of the labeling package. The established name is correct and consistent between the Prescribing Information and Patient Labeling. In addition, the following information is accurately included in the indicated insert:

- Route of administration (both inserts)
- Dosage and administration instructions/precautions (both inserts)
- Manufacturers information (both inserts)
- Storage and handling instructions/precautions (instruction for use insert)

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

75 mg granules - Per amendment received 11/12/2019

300 mg granules - Per amendment received 11/12/2019

Item	Information Provided in the NDA	Assessor's Comments
Proprietary name; established name, and dosage form	PROCYSBI; Cysteamine bitartrate delayed-release oral granules	**Adequate:** font size and prominence are now satisfactory
Dosage strength	75 mg or 300 mg	**Adequate**: Both container labels illustrate the strengths prominently next to the proprietary name.
Route of administration	Oral	**Adequate**: the oral ROA is specified in the established name. ***Note:*** *may change as a result of comment 1*
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	**75 mg packets**: Each packet contains: 221 mg cysteamine bitartrate equivalent to 75 mg cysteamine **300 mg packets**:	**Adequate**: The strengths of the sachets are based on historical/clinical exceptions stipulated in the current salt policy. The equivalency statements on the container label are acceptable.

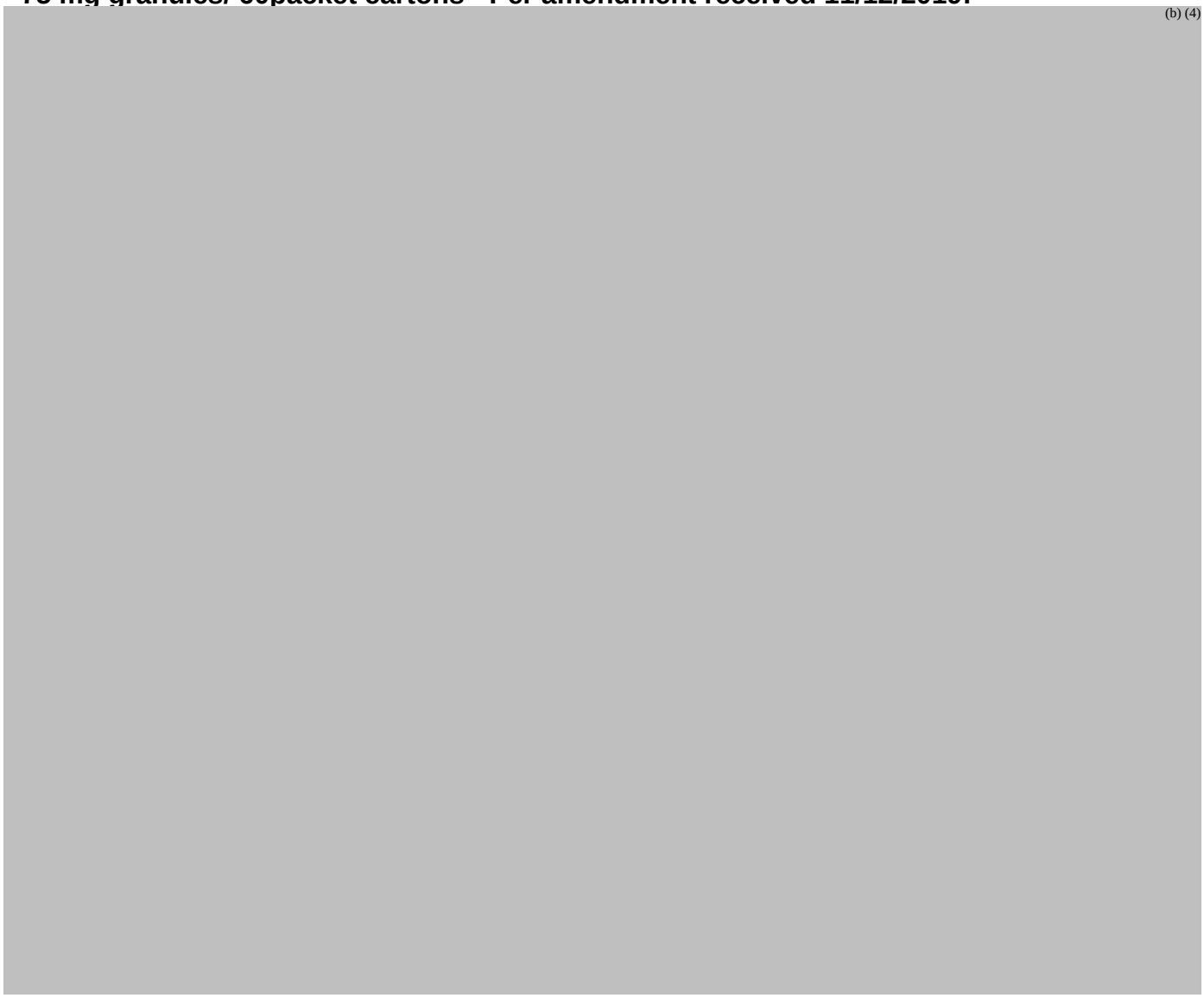
	Each packet contains: 884 mg cysteamine bitartrate equivalent to 300 mg cysteamine	
Net contents (e.g. tablet count)	n/a	The sachets are single use dosing units. Net contents are not needed on the container label.
"Rx only" displayed on the principal display	Yes	**Adequate**
NDC number	Not included	**Adequate**: Due to space restrictions on the container labeling, Horizon proposes to only display the NDC number and barcode on the carton, which is the smallest saleable unit. The carton is sold directly to patients and the carton contains the statement "Dispense only in original packaging" to ensure compliance. This product is also not intended to be sold to or used in hospitals.
Lot number and expiration date	Yes	**Adequate:** lot number and expiration date will be embossed on the crimped end of the tubes.
Storage conditions. If applicable, include a space on the container labeling for the user to write the new BUD.	Storage condition statement included	**Adequate**: the statement, (b) (4) [redacted] Is included
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	Drug product is not an injectable dosage form
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	No other package terms included
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	Drug product does not contain alcohol
Bar code	Not included	**Adequate**: Not included - the carton, which is the smallest saleable unit
Name of manufacturer/distributor	Included	**Adequate**: The distributors name has been added.
No text on Ferrule and Cap overseal	n/a	The sachets (packets) do not have a cap

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	The drug substance and product are not compendial

3.2 Carton Labeling

75 mg granules/ 60packet cartons - Per amendment received 11/12/2019:

(b) (4)



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(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	PROCYSBI; Cysteamine bitartrate delayed-release oral granules	**Adequate**: font size and prominence are satisfactory
Dosage strength	75 mg or 300 mg	**Adequate**: Both carton labels illustrate the strength prominently next to the proprietary name.
Route of administration	Oral	**Adequate**: the oral ROA is specified in the established name. ***Note:*** *may change as a result of comment 1*
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	**75 mg carton (front)**: Each packet contains: 221 mg cysteamine bitartrate equivalent to 75 mg cysteamine **300 mg carton (front)**:	**Adequate:** The strength of the sachets is based on cysteamine free base, consistent with current salt policy. The equivalency statements on the front of the carton label are acceptable.

	Each packet contains: 884 mg cysteamine bitartrate equivalent to 300 mg cysteamine	
Net contents (e.g. tablet count)	Contains 60 packets, or contains 120 packets	**Adequate**: Both dosage form strengths come in cartons containing either 60 or 120 packets. The carton labels for each strength differ only in packet count
"Rx only" displayed on the principal display	Yes	**Adequate**: "Rx only" is displayed an all carton sides containing the proprietary name
NDC number	75 mg, 60 packets: 75987-(b)(4)-13 75 mg, 120 packets: 75987-(b)(4)-14 300 mg, 60 packets: 75987-(b)(4)-13 300 mg, 120 packets: 75987-(b)(4)-14	**Adequate**: NDC numbers provided for each strength and carton size
Lot number and expiration date	Expiration date: Yes Lot number: **Yes**	**Adequate**: A prominent box for the expiration date is included on all carton labels. A box has been added containing the Lot number and expiration date in the appropriate formate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**Attention Pharmacist:** Prior to dispensing must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Dispense PROCYSBI with a 4 month discard date. **Attention Patient**: Store at room temperature, 20°C to 25°C (68°F to 77°F). Protect from light and moisture. Discard unused packets on "discard after" date	**Adequate**: Storage conditions for pharmacists and patients are included. Special storage statements; protection from light and moisture, and a discard statement are included under the patient storage statement.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	Drug product is not an injectable dosage form
Other package terms which require "Not for direct infusion" statement.	n/a	No other package terms included
If alcohol is present, must provide the amount of alcohol in terms of percent	n/a	Drug product does not contain alcohol
Bar code	Yes	**Adequate**: Included on all cartons
Name of manufacturer/distributor	Horizon Pharma USA, Inc., Lake Forest, IL 60045, Country of origin: Italy	**Adequate:** The distributor name is on the side label of each carton

No text on Ferrule and Cap overseal	n/a	The sachets (packets) do not have a cap
When a drug product differs from USP standard in strength, quality, or purity, as determined by compendial tests, and acceptance criteria, its difference shall be plainly stated on its label.	n/a	The drug substance and product are not compendial

Assessment of Carton and Container Labeling: Adequate

Deficiency 1 from the information request issued on 10/21/2019:
Please enhance the prominence of the API portion of the established name on the container labels. The boldness of the font should match the dosage from portion of the established name.

Applicant's response submitted via email on 10/24/2019:
Horizon commits to enhancing the prominence of the API name "cysteamine bitartrate" to bold font to match the dosage form of "delayed-release oral granules". The updated containers labels are included in this submission in Module 1.14.1.

Reviewer assessment:
The boldness of the font of the API portion established name now match the dosage from portion. **Satisfactory.**

Deficiency 2 from the information request issued on 10/21/2019:
The following information should be included on both container labels;

- NDC numbers,
- Drug product storage conditions,
- Bar codes, and
- The distributor's name.

Applicant's response submitted via email on 10/24/2019:
The container labels represent the individual (b) (4) packet which are not for individual sale. To ensure compliance, the statement "Dispense only in original packaging" is prominently stated on the carton label below the product strength. Horizon considered including additional information on the (b) (4) packet container label, but was unable to accommodate all information in the small packet size of 70 mm x 23 mm. Horizon commits to adding the name of the distributer in alignment with 21 CFR 210(i) for small packages. The updated containers labels are included in this submission in Module 1.14.1. For the initial product launch, Horizon proposes to use the container labels submitted in NDA 213491 Sequence 0001.

Reviewer assessment:
Horizon added the name of the distributer in alignment with 21 CFR 210(i) for small packages. The container label also includes the following statement: (b) (4) (b) (4) Due to space restrictions NDC numbers

and barcodes are not included on the container label. NDC number and barcode on the carton, which is the smallest saleable unit. The carton is sold directly to patients and the carton contains the statement “Dispense only in original packaging” to ensure compliance. DMEPA considers the updated container label acceptable. **Satisfactory.**

Deficiency 3 from the information request issued on 10/21/2019:
The location of the lot number is on the side panel with the barcode and is indicated by a purple box as shown in the figure below. The purple box is for mock-up purposes only and represent the location where the lot number, expiration date, GTIN and S/N will be printed in (b) (4) text on (b) (4) background.

Applicant’s response submitted via email on 10/24/2019:
The location of the lot number is on the side panel with the barcode and is indicated by a purple box as shown in the figure below. The purple box is for mock-up purposes only and represent the location where the lot number, expiration date, GTIN and S/N will be printed in (b) (4) text on (b) (4) background.

Reviewer assessment:
Lot number, expiration date, GTIN and S/N will be printed in purple box indicated by the red arrow. On 11/12/2019 the applicant submitted updated carton labels illustrating the proposed format for the above-mentioned numerical information. The updated labels can be found in the white space above the carton label summary table. DMEPA considers the updated container label acceptable. **Satisfactory.**

Applicant’s proposal (b) (4) was received via email on 10/21/2019:

Summarized history of container label proposal:

1. The applicant argued, [redacted] (b) (4) See **appendix 1** for applicants' proposal via email.
2. After discussion with secondary reviewer, Moo-Jhong Rhee, we decided [redacted] (b) (4) See **appendix 1** for IR response emails.
3. The applicant, Horizon Pharma, anticipates [redacted] (b) (4) This time frame is acceptable from an OPQ perspective. See **appendix 2** for IR response via email.
4. On October 30th the clinical team confirmed [redacted] (b) (4) See **appendix 3** for clinical concurrence via email.
5. The DMEPA team expressed additional concern with both the container and carton labels. They issued an IR expressing those concerns, to which the applicant's response and updated label images were received on 11/12/2019.
6. DMEPA has approved the updated carton and container labels. However, regarding the applicant's proposal [redacted] (b) (4), DMEPA declined the proposal since at least two of the implemented recommendations were based on the CFR, and all are in FDA guidance documents for industry, See **appendix 4** for DMEPA's recommendation via email.
7. After further discussion on the proposal between OPQ/ONDP, DMEPA, and OND/DGIEP, OND has decided to concur DMEPA's recommendation to deny the proposal [redacted] (b) (4) See appendix 5 for the email chain documenting this discussion.

4.0 List of Deficiencies: none

Overall Assessment and Recommendation:

The Prescribing Information and container/carton labels in NDA 213491 are deemed adequate, and therefore, this NDA is recommended for **Approval** from the CMC Label and Labeling perspective.

Primary Labeling Assessor Name and Date:

Ryan Holland, Ph.D.
Reviewer, DNDP II/ONDP/OPQ

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Holland's assessment on the labeling and labels with satisfactory resolution of all previously noted deficiencies, and therefore, I concur with his recommendation of **Approval** of this application from the CMC labeling perspective.

Moo-Jhong Rhee, Ph.D.

Chief, Branch V, DNDP II/ONDP/OPQ

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Moo Jhong Rhee

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Ryan Holland

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213491
Assessment Cycle Number	1
Drug Product Name/ Strength	PROCYSBI® (Cysteamine bitartrate) delayed-release oral granules, 75 mg, 300 mg
Route of Administration	Oral
Applicant Name	Horizon Pharma USA, Inc.
Therapeutic Classification/ OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
RLD Number	NDA 203389
Proposed Indication	Treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older

Assessment Recommendation: **Adequate**

Assessment Summary:

PROCYSBI delayed-release oral granules (granules) in packets is a new dosage form as an alternate packaging configuration for patients with a gastrostomy tube or who administer contents of capsules with food or liquid.

The applicant has an approved NDA 203389 for 25 mg and 75 mg capsules containing delayed release granules. This NDA used the same granules of the approved capsule products to fill 75 mg or 300 mg of granules into packets.

The dissolution method and acceptance criteria are acceptable. The risk of dissolution failure is low as the same granules in approved NDA 203389 are used.

From Biopharmaceutics perspective, NDA 213491 is adequate.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Application 213491 - Sequence 0001 - 0001 (1) 05/16/2019 ORIG-1 /New/NDA	**5/16/2019**

Application 213491 - Sequence 0006 - 0006 (10) 08/02/2019 ORIG-1 /Quality/Response To Information Request	**8/2/2019**

Highlight Key Issues from Last Cycle and Their Resolution:

- Justification for increasing the rotational speed from 75 rpm in the 75 mg dissolution method to 150 rpm for the 300 mg dissolution.
  Resolution: The applicant justified the increased rotation speed (b) (4) (b) (4) (b) (4) The justification is acceptable.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Dissolution Method

The dissolution method for the 75 mg granules in packets is the same as the approved dissolution method for PROCYSBI delayed-release capsules (capsules), 25 mg and 75 mg, in NDA 203389. The dissolution method for 300 mg granules in packets is identical to the method for 25 mg capsules, 75 mg capsules and 75 mg granules in packets except for the differences described below:

(b) (4)

for the 300 mg strength, the speed was increased from 75 RPM to 150 RPM. (b) (4) (b) (4)

No additional changes were made to the dissolution method for the 300 mg strength and the method was validated per ICH guidance as summarized in the validation of analytical procedure report Dissolution 300 mg RPT77170 in Section 3.2.P.5.3 [Granules, All] submitted in Sequence 0001.

a dissolution profile comparison of the 3 process validation lots of 75 mg granules in packet at 75 RPM versus 300 mg granules in packet at 150 RPM is provided in Figure 1. The graphs demonstrate there is no difference in the dissolution profile.

Figure 1 PROCYSBI Delayed-Release Oral Granules Dissolution Profile Comparison (n = 3)

The proposed two-stage dissolution method is shown below.

Acid Stage

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
I	75 rpm (75 mg) 150 rpm (300 mg)	1000 mL	37°C	0.1 N HCl

Basic Buffer Stage

USP Apparatu	Rotation Speed	Medi a	Temp	Medium
I	75 rpm (75 mg) 150 rpm (300 mg)	1000 mL	37°C	0.2 M sodium phosphate buffer pH 6.8

Dissolution Acceptance Criteria

The proposed dissolution acceptance criteria for the 7 mg and 300 mg packets are shown below:

Acid Stage: NMT (b) (4)% at 2 hr

Buffer Stage: Q = (b) (4)% at 20 minutes

Assessment: *Adequate*

Dissolution Method
The dissolution method for the 75 mg granules in packets is the same as the approved dissolution method for the granules in PROCYSBI delayed-release capsules (capsules), 25 mg and 75 mg, in NDA 203389. The dissolution method was found to be adequate in NDA 203389 (Kareen Riviere on 2/14/2013).

The dissolution method conditions of the 300 mg granules are the same as those of 75 mg granules except the higher rotational speed of the basket to (b) (4) The justification for increasing the rotational speed is acceptable. In fact, the 300 mg granules have the same composition as the 75 mg granules; the only difference is (b) (4) The applicant demonstrated that the dissolution of the 300 mg granules was comparable to that of the 75 mg (b) (4) The dissolution method of the 300 mg granules is acceptable.

Dissolution Acceptable Criteria
The applicant proposed acceptance criteria for the Acid Stage (NMT (b) (4)% at 2hr) and the Buffer Stage (Q = (b) (4)% at 20 min) are acceptable.

Biowavier Information

The applicant did not submit a biowavier request in this submission. The applicant stated that bioequivalence studies (RP103-02, RP103-05 and

RP10306) submitted in the original NDA 203389 support sprinkling the contents of the capsules on food/liquid with the persistence of the delayed effect.

The dosing regimen of the granules in packet and the granules in capsule is the same.

Table 1: Starting and Maintenance Dosage of PROCYSBI by Body Weight in Cysteamine-Naïve Patients 1 Year of Age and Older (Dosage Rounded Using Available Capsule or Oral Granules in Packet Strengths)

Weight in kilograms	Starting PROCYSBI Dosage in mg every 12 hours, as a Fraction of the Maintenance Dosage		Maintenance PROCYSBI Dosage in mg every 12 hours*
	1/6 of dosage	1/4 of dosage	
5 or less	25	50	200
6 to 10	50	75	300
11 to 15	75	100	400
16 to 20	100	125	500
21 to 25	100	150	600
26 to 30	125	175	700
31 to 40	125	200	800
41 to 50	150	225	900
51 kg and greater	175	250	1000

* Higher dosages may be required to achieve target therapeutic WBC cystine concentration *[see Dosage and Administration (2.4)]*.

B. 13 BIOWAIVER REQUEST

Assessment: *Adequate*

The applicant did not submit a biowavier request. No clinical studies were performed for this NDA. The applicant relies on the clinical trials in NDA 203389 to bridge the efficacy and safety of the granules. Also, both the capsules containing the granules and the packets containing the granules will deliver the same granules and doses to the patients in the same final forms (granules) to be sprinkled to soft foods or dispersed in a drink. The adequacy of relying on NDA 203389 to bridge this NDA will be reviewed by Clinical Reviewer and Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments

Assessment: *N/A*

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Vincent Li, Ph.D., 08/30/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Vincent Li

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	PROCYSBI® (Cysteamine Bitartrate)
NDA Number	213491
Assessment Cycle Number	1
Drug Product Name/ Strength	PROCYSBI® (Cysteamine Bitartrate) Delayed-Release Oral Granules, 75 mg and 300 mg
Route of Administration	oral
Applicant Name	Horizon Pharma, Inc.
Therapeutic Classification/ OND Division	Division of Gastroenterology and Inborn Errors Products
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile drug product

Assessment Recommendation: **Adequate**

Assessment Summary: **No microbiology deficiencies were identified. This submission is recommended for approval on the basis of sterility assurance.**

List Submissions being assessed (table):

Document(s) Assessed	Date Received	Assigned to Reviewer
5/16/2019	5/16/2019	5/30/2019

Highlight Key Issues from Last Cycle and Their Resolution: NA

Remarks: NA

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): NA

Supporting Documents: NA

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

NDA 213491: The granules form of delayed-release formulation of cysteamine bitartrate is now being proposed to be packed in packet (Procysbi, delayed-release oral granules).

Previously approved referenced NDA: NDA 203389- Procysbi delayed-release capsules containing the granules form of delayed-release formulation of cysteamine bitartrate.

Comparison of NDA 203389 and NDA 213491 drug products:

a) The proposed granules in **packets** are the same granules as those contained within PROCYSBI delayed-release **capsules** described in NDA 203389 which are approved to be taken whole or opened to administer the contents of capsules.
b) Proposed NDA 213491-Procysbi delayed-release granules in packet (cysteamine bitartrate) are in **75mg and 300 mg** strength.
NDA 203389-Procysbi delayed -release capsules are **25mg and 75 mg** strength.

Manufacturer: (b) (4)
(b) (4)

Manufacturing process development: (b) (4)
(b) (4)

Container closure system: Procysbi delayed-release oral granules (granules), 75 mg and 300 mg, are in packets (b) (4)

Specifications:

Test	Test Method	Acceptance Criteria	Exhibit Batch Results (75mg) 19082333 and 19082334	Exhibit Batch Results (300mg) 19082335
Microbial limits	(b) (4) TP76382	Total Aerobic Microbial Counts: NMT (b) (4) CFU/g	(b) (4) CFU/g	
		Total Yeasts and Molds Counts: NMT (b) (4) CFU/g	(b) (4) CFU/g	
		Escherichia coli: absent/g	Absent/g	

Applicant has provided method suitability test for microbial limits.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). A validation study summarized in RPT76519 in Section 3.2.P.5.3 [Granules, All] was performed (b) (4) to demonstrate the method suitability of a Harmonized USP/Ph.Eur./JP microbiological examination of non-sterile products for the 300 mg granules in a packet container closure system. This validation supports the 75 mg granules in packet as the 300 mg strength is worst case. Results from the validation are provided (P. 5.3- validation-analytical-procedure.pdf).

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for microbial limits as part of the post-approval stability protocol (timepoints are given in the table below). The microbial limits stability acceptance criteria is the same as those specified for release. Bioburden: acceptance criteria: less than (b) (4) CFU/g.

Table: PROCYSBI Delayed-Release Oral Granules Post-Approval Stability Protocol

(b) (4)

The proposed shelf life for PROCYSBI delayed-release oral granules, 75 mg and 300 mg, is a cumulative 24 months, with the product being stored under refrigerated conditions at 5°C prior to dispensing and for 4 months at room temperature (20°C to 25°C) post-dispensing.

Drug product is single use. The granules are sprinkled from the capsule(s) or packet(s) on applesauce, berry jelly or fruit juice (except grapefruit juice) and the mixture (food/drug combination) has to be swallowed within 30 minutes of preparation.

Assessment: *Adequate*
The microbiological quality of the drug product is controlled via a suitable testing protocol. The Microbial Limits specification for "Procysbi delayed-release oral granules" complies with USP <1111> and is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Primary Microbiology Assessor Name and Date: Nutan Mytle, Ph.D. 8/13/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal Sweeney, Ph.D. 9/7/2019

Neal Sweeney

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Nutan Mytle

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Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 213491
Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg and 300 mg

Product Attribute / CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	LifeCycle consideration/Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters	L		Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Low to None	None
Packet Seal Integrity	Sealing parameters	L		Low to None	None

Hitesh Shroff

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