

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213491Orig1s000**

**SUMMARY REVIEW**

## Division Director and Clinical Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	<ul style="list-style-type: none"> <li>• Anita Zaidi, MD, Clinical Reviewer, Division of Gastroenterology and Inborn Errors Products (DGIEP)</li> <li>• Joette Meyer, PharmD, Cross Discipline Team Leader (CDTL), DGEIP</li> <li>• Lisa Soule, MD, Associate Director, DGIEP</li> </ul>
<b>Subject</b>	Division Director and Clinical Summary Review
<b>NDA/BLA # and Supplement #</b>	NDA 213491*
<b>Applicant</b>	Horizon Pharma
<b>Date of Submission</b>	5/16/2019
<b>PDUFA Goal Date</b>	3/16/2020
<b>Proprietary Name</b>	Procysbi
<b>Established or Proper Name</b>	Cysteamine bitartrate
<b>Dosage Form(s)</b>	Delayed-release oral granules: 75 mg and 300 mg in unit-dose packets
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older
<b>Action or Recommended Action:</b>	Approval
<b>Approved/Recommended Indication(s)/Population(s)</b>	Same as above

\* The Applicant initially submitted the information on Procysbi delayed-release oral granules as a supplement to the NDA for delayed-release capsules (NDA 203389/S-023) on February 28, 2019. It was determined that the submission should be submitted as a new original NDA.

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers/Team Lead</b>
OND Action Package, including:	
CDTL Review	Joette Meyer
Clinical	Anita Zaidi/Patroula Smpokou
OPQ Review	Hitesh Shroff
ATL/RBPM	Hitesh Shroff/LCDR Oumou Barry
Microbiology	Nutan Mytle/Neal Sweeney
Drug Process	Ryan Holland/Moo Jhong Rhee
Drug Substance	Fredrich Burnett/Donna Christner
Process/Facilities	Kejun Chen/Yaodong (Tony) Huang
Biopharmaceutics	Vincent Li/Tapash Ghosh
OPDP	Adewale Adeleye
OSE/DMEPA	Lissa Pringle-Owens/Idalia Rychlik
DMPP	Nyedra Booker/Marcia Williams-Britt

OND=Office of New Drugs  
 OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSE=Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DMPP=Division of Medical Policy Programs

## 1. Benefit-Risk Assessment

The benefit-risk of Procysbi (cysteamine bitartrate) delayed-release oral granules for the treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older has not changed with submission of this new NDA adding a new dosage form: delayed-release oral granules. Therefore, on the basis of the information discussed in the remainder of this review, approval of this NDA is recommended.

Procysbi delayed-release oral granules in unit-dose packets is a new dosage form as well as an alternate packaging configuration for Procysbi. The oral granules are supplied in dosage strengths of 75 mg and 300 mg, as compared to the currently approved capsules available in strengths of 25 mg and 75 mg. The Applicant developed the 300 mg strength for patients requiring higher dosage, as fewer packets are needed to achieve the required dose. The granules are the same granules as those contained within capsules (NDA 203389), which are approved to be swallowed whole or the capsules opened and the contents sprinkled on applesauce, berry jelly or fruit juice (except grapefruit juice) liquid. Comparative bioavailability studies support sprinkling the contents of the capsules on food/liquid and persistence of the delayed-release effect.

This NDA contains only chemistry, manufacturing and controls (CMC) data. Supportive CMC, nonclinical, clinical pharmacology, and clinical information can be found in NDA 203389. No clinical efficacy or safety data were submitted. Postmarketing safety data for Procysbi delayed-release capsules were reviewed and no new safety signals were identified.

In the original submission of NDA 203389, the Applicant conducted a relative bioavailability study (Study RP103-05) in healthy subjects with a dosage of 600 mg of Procysbi and demonstrated that the  $C_{max}$  and AUC were comparable between the two dosage forms and modes of administration: opening the capsules and sprinkling the granules on applesauce versus swallowing the capsules intact with water. Thus, it is acceptable for the Applicant to cross-reference and rely on the information in NDA 203389 for Procysbi delayed-release capsules to support approval of the delayed-release oral granules with the same indication and dosage regimen.

NDA 203389 is a 505(b)(2) application relying on Cystagon (cysteamine bitartrate) capsules (NDA 020392) as the listed drug. Cystagon is an immediate-release formulation of the same active moiety. NDA 213491, which cross-references NDA 203389, also relies on Cystagon (NDA 020392). The bridge for NDA 203389 to Cystagon is captured in the assessment form for NDA 203389: “The applicant bridged the proposed product to the reference product through assessments of assay and impurity profiles and pharmacokinetic/pharmacodynamic studies performed in patients with nephropathic cystinosis, and bioequivalence studies in healthy volunteers.” The bridge for Procysbi delayed-release capsules in NDA 203389 is relevant to support approval of NDA 213491. Procysbi delayed-release oral granules, the proposed product in NDA 213491, (b)(4) has comparable relative bioavailability to Procysbi delayed-release capsules in NDA 203389.

## 2. Background

### Nephropathic Cystinosis

Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder characterized by accumulation of the amino acid cystine in almost all cells. It has been found in all ethnic groups and has an estimated prevalence of 1:100,000-200,000.<sup>1</sup> The disorder affects an estimated 500 individuals in the US. It is caused by mutations of the CTNS gene, which encodes the lysosomal cystine carrier cystinosin. However, the pathogenesis of the disease remains unknown. Classic nephropathic cystinosis (early onset or infantile) is the most common of three variants of the disease, with onset of disease within the first year of life. Intermediate nephropathic cystinosis (juvenile/late onset) shares all of the clinical features of classic nephropathic cystinosis, with onset typically, after 10 years of age. The third variant, non-nephropathic (adult) cystinosis, is characterized by ocular involvement only. Some genotypes are more commonly associated with a particular variant (e.g., truncating CTNS mutations and classic disease). However, phenotypic differences have been described between members of the same family.<sup>2</sup>

Clinical features of the disease include impaired renal function, renal Fanconi syndrome, growth failure, hypophosphatemic rickets, hypothyroidism, and primary hypogonadism in males. Nephropathic cystinosis is the major cause of inherited Fanconi syndrome. Presenting features in infants include signs of Fanconi syndrome before age 6 months and growth failure from age six months onward. Onset of corneal involvement may also start within the first year of life and clinical evidence of corneal disease (cystine crystals present on slit lamp examination) is always present by age 16 months. Patients with intermediate cystinosis may have absent or mild Fanconi syndrome and corneal events during childhood. However, progression to end-stage renal disease universally occurs, typically, between age 15 and 25 years.

Prior to the development of cystine-depleting therapy, renal transplantation was demonstrated to stabilize or prolong renal function and overall survival in nephropathic cystinosis patients.<sup>3</sup> Cystine crystals do not accumulate in kidney allograft tissue; however, pre-existing renal tubular damage in the host kidney is irreversible. Renal transplantation does not alter the course of non-renal disease.

Cysteamine is an amino thiol 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 lysosomes, thereby decreasing the intra-lysosomally stored cystine in patients with nephropathic cystinosis.

---

<sup>1</sup> Nesterova G, Gahl WA, Cystinosis, GeneReviews™- NCBI Bookshelf  
<http://www.ncbi.nlm.nih.gov/books/NBK1400/>

<sup>2</sup> Wilmer MJ, Schoeber JP et al, Cystinosis: practical tools for diagnosis and treatment, *Pediatr Nephrol* 2011; 26:205-215.

<sup>3</sup> Almond PS, Matas AJ et al, Renal transplantation for infantile cystinosis: long-term follow-up, *J Pediatr Surg* 1993; 28(2):232-8.

### Current Therapy

The current standard of care for nephropathic cystinosis is treatment with a cystine-depleting agent (cysteamine bitartrate) to decrease cellular deposits of cystine, with initiation of treatment as soon as possible after diagnosis. Cystine depletion therapy slows progression of both renal and non-renal disease. Therefore, cysteamine is recommended for all nephropathic cystinosis patients, regardless of transplantation status. Measurement of white blood cell (WBC) cystine levels is used for disease diagnosis and to monitor treatment response. Therapeutic goals target a near-normal WBC cystine levels (normal = 0.2 nmol ½ cystine/mg protein).<sup>4</sup> Supportive care for nephropathic cystinosis focuses on management of renal and non-renal disease manifestations. Renal disease management includes treatment of renal Fanconi syndrome and renal transplantation for patients with end-stage renal disease. Non-renal disease management may include nutritional support, growth hormone and thyroid hormone replacement, carnitine supplementation, and gastrostomy feedings.<sup>5</sup>

### Regulatory History

Procysbi (cysteamine bitartrate) delayed-release capsules (NDA 203389) was approved April 3, 2013 for the treatment of nephropathic cystinosis in adults and children age 6 years and older, submitted as a 505(b)(2) submission referencing Cystagon (cysteamine bitartrate) capsules (NDA 20392), an immediate-release formulation of cysteamine bitartrate approved in 1994, as the listed drug. Procysbi capsules are a (b) (4) formulation of the bitartrate salt of cysteamine, encapsulated in hard gelatin and available in strengths of 25 mg and 75 mg of cysteamine. Procysbi was developed to allow for twice-daily administration. Cystagon is administered every 6 hours around the clock, making patient adherence to the regimen difficult. The starting and maintenance dosage of Procysbi is based on body weight of the patients. It ranges from 25 mg to 1000 mg every 12 hours. Thus, a typical dosage would range from one to more than thirteen capsules every 12 hours.

The original approval for Procysbi relied on the Agency's prior findings of safety and effectiveness for Cystagon. Approval of Procysbi was based on a 9-week, open-label, randomized, cross-over, non-inferiority trial (RP103-03) evaluating pharmacokinetics, pharmacodynamics, efficacy and safety of Procysbi compared to Cystagon in patients with nephropathic cystinosis 6 years of age and older who were on a stable dosage of Cystagon. The trial demonstrated that Procysbi was non-inferior to Cystagon with respect to the depletion of WBC cystine concentrations, the primary endpoint. Measurement of WBC cystine concentration is used to monitor treatment response. See clinical review by Carla Epps dated April 26, 2013.

Comparative bioavailability studies (RP103-02, RP103-05, RP103-06) in the original NDA 203389 supported oral administration by opening the capsules and sprinkling the contents of the capsules on food/liquid. In addition, the Applicant provided information from a clinical study (RP103-04) on administration of Procysbi capsule contents mixed with applesauce and

---

<sup>4</sup> Kleta R, Kaskel F et al, First NIH Office of Rare Diseases Conference on cystinosis: past, present, and future, *Pediatr Neph* 2005; 20: 452-454

<sup>5</sup> Yeagy BA, Harrison F et al, Kidney preservation by bone marrow cell transplantation in hereditary nephropathy, *Kidney Int* 2011; 79:1198-1206

administered through a gastrostomy feeding tube size 12 French and larger that supported labeling for administration of the capsule contents through a gastrostomy tube.

In 2015, the indication for Procysbi was extended to pediatric patients 2 to less than 6 years of age based on data from an open-label, extension trial (RP103-04), which included 13 patients aged 2 to 6 years who were previously on a stable Cystagon dosage and who were switched to Procysbi (NDA 203389/S-010). See clinical review by Lauren Weintraub dated August 13, 2015.

In 2017, the indication for Procysbi was further expanded include pediatric patients of 1 year of age and older based on data from an open-label trial (RP103-08), which included 15 patients aged 1 to 6 years of age (NDA 203389/S-020). See clinical review by Wen-Yi Gao dated December 1, 2017.

On February 28, 2019, the Applicant submitted a Prior Approval Supplement (S-023) to NDA 203389 for the addition of an alternate packaging configuration for Procysbi delayed-release oral granules in unit-dose packets of 75 mg and 300 mg to make it more convenient for patients who cannot swallow the intact capsules. The oral granules contain the same delayed-release granules as in the capsules. In the NDA supplement, the Applicant provided detailed CMC information including composition, manufacturing process, container closure system, stability data and labeling. The Applicant relied on the clinical trials in NDA 203389 to support the efficacy and safety of the oral granules.

FDA determined that although the delayed-release granules are the same in Procysbi capsules and unit-dose packets and can both be administered by sprinkling on soft food or mixing with liquid, the capsule and packet are two different dosage forms because their formulations are not qualitatively and quantitatively equivalent from the CMC perspective. In case of the capsule, the gelatin shell is considered as part of the drug product; thus, the ingredients are different for the oral granules without the gelatin capsule. FDA requested the Applicant to withdraw the pre-approval supplement and submit the marketing application for Procysbi delayed-release oral granules in unit-dose packets of 75 mg and 300 mg as a new NDA.

The Applicant was notified on April 10, 2019 that a new NDA for Procysbi delayed-release oral granules was needed. The Applicant withdrew NDA 203389/S-023 on April 26, 2019. The new NDA 213491 was submitted on May 16, 2019.

### **3. Product Quality**

The proposed dosage strengths for Procysbi delayed-release oral granules are 75 mg and 300 mg cysteamine. The 300 mg strength is higher than the 25 mg and 75 mg approved strengths for Procysbi delayed-release capsules. The delayed-released granules are the same in both capsule and packet dosage forms.

The OPQ review concludes that the Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed Procysbi delayed-release oral granules,

75 mg or 300 mg in unit-dose packets. The recommendation is for approval and includes an overall approval recommendation for the manufacturing facilities.

The following is a summary of the OPQ review:

#### Drug Substance

Detailed information is provided in the cross-referenced NDA 203389. The overall quality of cysteamine bitartrate is assured by its specification, all potential impurities are controlled per ICH Q3A, and the analytical methods were validated. The OPQ drug substance review concludes the submitted information is adequate to support the drug product.

#### Drug Product

Cysteamine bitartrate (b) (4)

The approved (b) (4) granules manufacturer (b) (4) and testing sites (b) (4) for the capsules were also proposed for the granules in packet. (b) (4) is the proposed facility to package the (b) (4) granules directly into packets.

The container closure (packet) for the granules consists of a (b) (4)

(b) (4) The container closure was selected (b) (4) The referenced DMF was deemed adequate by OPD.

The OPQ drug product review concluded the release and stability specifications and other supporting data are sufficient to ensure the identity, strength, purity, and quality of the drug product during the proposed shelf life of 24 months.

This submission included 12-month long-term (5° C) stability data, 6 months accelerated stability data (25° C), and a comparability study with the first 6 months of the capsule dosage form. The Applicant proposed a 24-month expiration dating period that is consistent with the approved shelf-life of the capsules. OPQ agreed with the 24-month expiration date when the drug product is stored at 5°C in the proposed container closure system.

As a post-approval stability commitment, the Applicant has agreed to complete stability testing; at this time, the release and stability specifications are sufficient and appropriate to insure the quality of the drug product.

#### Microbiology (Sterility Assurance)

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 by OPQ microbiology review.

### Manufacturing and Facilities

The drug product manufacturing process was found to be acceptable by OPQ. The Office of Process and Facilities (OPF) 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.

### 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 was deemed acceptable by OPQ.

### Biopharmaceutics

The drug product dissolution method is the same as the one used in NDA 203389. However, for 300 mg oral granules packets, the rotation speed was increased [REDACTED] (b) (4) [REDACTED]. The drug product dissolution method development, dissolution method, dissolution data and dissolution specification were deemed adequate by OPQ biopharmaceutics review.

### Labeling

See Section 12.

## **4. Nonclinical Pharmacology/Toxicology**

No nonclinical information was submitted with this NDA.

## **5. Clinical Pharmacology**

No clinical pharmacology information was submitted with this NDA.

## **6. Clinical Microbiology**

The submission is recommended for approval on the basis of sterility assurance; see Section 3.

## **7. Clinical/Statistical-Efficacy**

No efficacy studies were conducted for this NDA.

## **8. Safety**

No safety studies were conducted for this NDA. Refer to previous clinical reviews for NDA 203389 and the Procysbi label for the most updated safety information.



### Post-Marketing Experience

Periodic Adverse Drug Experience Report (PADER) for Procysbi NDA 203389 covering April 30, 2018 to April 29, 2019 was reviewed. The Periodic Benefit-Risk Evaluation Report (PBRER) covering April 30, 2018 to August 15, 2019 was also reviewed.

Most reported events are consistent with known adverse reactions to Procysbi.

Gastrointestinal symptoms consistently represented the most commonly reported events. Other frequently reported events included abnormal skin odor and headaches.

Among the non-serious unexpected events, malaise, amino acid level increase, arthralgia and nasopharyngitis were the most commonly reported events. However, these events are also commonly reported as disease symptoms in patients with nephropathic cystinosis and are also commonly reported in the general population; therefore, there is insufficient evidence that there is a causal relationship between these events and Procysbi.

Two fatal cases were reported during the reporting period.

- 40-year-old female with history of cystinosis, kidney transplant, depression, and bipolar disorder died approximately 2.5 years after initiation of Procysbi. The reported cause of death included kidney transplant rejection, organ failure and malnutrition. Organ failure resulting in death is a known adverse outcome resulting from kidney transplant rejection and it is unlikely that the outcome is related to Procysbi.
- 30-year-old female patient with history of advanced cystinosis requiring dialysis died following a respiratory infection caused by influenza, requiring mechanical ventilation. Complications from influenza are more common in patients receiving hemodialysis due to lowered immunity and multiple comorbidities; therefore, the causality is more likely related to the patient's underlying disease process than to Procysbi.

After review of the post-marketing reports, the information provided leads to the conclusion that the safety profile of Procysbi is consistent with the safety information in the product labeling. The introduction of the new dosage form proposed in this NDA is not expected to alter the safety profile.

## **9. Advisory Committee Meeting**

This application was not referred to an FDA Advisory Committee as no controversial issues that would benefit from advisory committee discussion were identified.

## **10. Pediatrics**

No pediatric studies were conducted as part of this NDA. Procysbi was granted orphan drug designation on October 24, 2006 for the treatment of nephropathic cystinosis; therefore, the Pediatric Research Equity Act does not apply. A Pediatric Written Request (WR) was used to obtain data in children less than 6 years of age. The WR was fulfilled and the Applicant was granted exclusivity December 22, 2107 with approval of NDA 203389/S-20.

## 11. Other Relevant Regulatory Issues

None

## 12. Labeling

### Prescribing Information

The Applicant has proposed a single Prescribing Information (PI) for both Procysbi dosage forms: delayed-release capsules and delayed-release oral granules.

- The CMC-related sections of labeling (Dosage Forms and Strengths, Description and Storage and Handling/How Supplied) have been revised to include the new dosage form (delayed-release oral granules) and the available strengths (75 mg and 300 mg unit-dose packets).
- The Dosage and Administration section has been updated to refer to both the capsules and oral granules, primarily regarding preparation and administration. Procysbi delayed-release oral granules should not be crushed or chewed. The granules can be sprinkled and mixed in applesauce, berry jelly or fruit juice (except grapefruit juice) and administered orally. For patients with a gastrostomy tube, the oral granules can be mixed in applesauce and administered through a bolus tube.
- The Patient Counseling Information section has been updated to include brief instructions on how to prepare and administer the oral granules, in addition to the capsules, and refers to the Instructions for Use document for complete patient instructions. Storage information was also added (protect from moisture and do not store the oral granules in opened packets).

### Patient Labeling (Patient Package Insert (PPI) and Instructions for Use (IFU))

- A collaborative review by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) of the Applicant's proposed PPI and IFU was completed December 3, 2019. DMPP also conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on October 11, 2019.
- The version of the IFU dated 12/13/2019 was found acceptable by DMPP and OPDP.
- The version of the PPI dated 1/20/2020 was found acceptable by DMPP and OPDP.

### Carton and Container Labeling

- Please see CMC labeling review by Dr. Ryan Holland for further information of the changes made to the carton and container labeling.
- DMEPA identified potential medication error issues with the submitted container labels and carton labeling in the initial review by Lissa Owens dated October 11, 2019.

- Revised container labeling and carton labeling were received from the Applicant on November 12, 2019 and DMEPA found them to be acceptable, noted in the review by Lissa Owens dated November 14, 2019.
- An additional IR was sent on December 11, 2019 with a request from OPDP (b) (4) (b) (4) The version of the carton submitted 12/17/19 was found acceptable by OPDP.
- Of note, the PI and carton/container labels are not consistent with each other with regard to the Salt Policy equivalency statement.
  - The carton/container labels state: “Each packet contains: 884 mg cysteamine bitartrate equivalent to 300 mg cysteamine.”
  - The PI states, “Each packet of PROCYSBI delayed-release oral granules contains either 75 mg cysteamine (equivalent to 221 mg cysteamine bitartrate) or 300 mg cysteamine (equivalent to 884 mg cysteamine bitartrate).

However, the PI and carton container labels are consistent with the previously approved Procysbi delayed-release capsules (NDA 203389). This NDA has the same discrepancy between the PI and carton container labels. OPQ accepts the discrepancy due to the historic precedent.

#### Proprietary Name Review

The Applicant requested the same proprietary name (Procysbi) for the new proposed dosage form as for the existing product. On October 9, 2019, DMEPA concluded the name is conditionally acceptable. See review by Sherly Abraham dated October 8, 2019.

The DMEPA review included the following considerations in their decision making:

We considered the appropriateness of using the proprietary name, Procysbi, for the oral granule formulation proposed under NDA 213491, which would represent a product line extension. We note that the Procysbi capsules and the proposed oral granules share the same active ingredient, indication, route of administration, dose and frequency of administration. Additionally, per the applicant, the proposed granules in the packets are the same granules as those contained in the currently marketed Procysbi delayed-release capsules, which are approved to be swallowed whole or opened to administer the contents of capsules. Per the applicant, the granule formulation is bioequivalent to the currently approved capsule formulation and the recommended dosage and frequency is the same for both dosage forms.

It is common and accepted practice to have a product line with multiple dosage forms share one proprietary name and, while we note the dosage forms are different, these differences can be managed via labeling. We note that both dosage forms have a shared strength (75 mg); however, provided that the review team confirms that these products are bioequivalent, can be substituted on a mg per mg basis, and have no clinically significant differences, we do not anticipate this product line extension will introduce medication errors related to switching between these dosage forms.

Furthermore, we have not retrieved any medication error name confusion reports involving Procysbi. Therefore, given the precedent for using a single proprietary name to market multiple dosage forms, we have no safety concerns with the proposal to market the granules with the proprietary name, Procysbi.

As noted above, the delayed-released oral granules are the same in both capsule and packet dosage forms. The recommended dosage and frequency are the same for both the capsules and the packets, although the packets are available in a higher strength (300 mg) than the capsules (25 mg and 75 mg). The products can be substituted for each other on a mg per mg basis and there are no clinically significant differences in the dosage forms.

### **13. Postmarketing**

A risk evaluation and mitigation strategy is not necessary for approval of this NDA. No new post-marketing requirements or commitments are required as part of this NDA.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

JOETTE M MEYER  
01/30/2020 04:29:15 PM

LISA M SOULE  
01/30/2020 04:36:09 PM