CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213491Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: December 11, 2019

To: Mimi Phan, Pharm.D., Senior Program Management Officer
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for PROCYSBI® (cysteamine bitartrate)

NDA: 213491

In response to DGIEP's consult request dated July 13, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for PROCYSBI® (cysteamine bitartrate) delayed-release oral granules (Procysbi).

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI/IFU received by electronic mail from DGIEP on November 27, 2019, and are provided below. OPDP has no comments on the proposed PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI/IFU were sent under separate cover on December 3, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 12, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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

PATIENT LABELING REVIEW

Date:	December 2, 2019
To:	Mimi T. Phan, PharmD Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	PROCYSBI (cysteamine bitartrate)
Dosage Form and Route:	delayed-release oral granules
Application Type/Number:	NDA 213491
Applicant:	Horizon Pharma USA, Inc.

1 INTRODUCTION

On May 16, 2019, Horizon Pharma USA, Inc. submitted for the Agency's review a New Drug Application (NDA) for PROCYSBI (cysteamine bitartrate) delayed-release oral granules, 75 mg and 300 mg (NDA 213491). The proposed delayed-release oral granules in packets are the same granules as those contained within PROCYSBI (cysteamine bitartrate) delayed-release capsules, for oral use approved on April 30, 2013 under NDA 203389.

PROCYSBI (cysteamine bitartrate) delayed-release oral granules and PROCYSBI (cysteamine bitartrate) delayed-release capsules, for oral use will share a combined label. PROCYSBI (cysteamine bitartrate) is a cystine-depleting agent indicated for the treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on July 13, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PROCYSBI (cysteamine bitartrate) delayed-release oral granules.

DMPP 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.

2 MATERIAL REVIEWED

- Draft PROCYSBI delayed-release oral granules PPI and IFU received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on November 18, 2019.
- Draft PROCYSBI delayed-release oral granules PPI and IFU received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on November 27, 2019.
- Draft PROCYSBI delayed-release oral granules Prescribing Information (PI) received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on November 18, 2019.
- Draft PROCYSBI delayed-release oral granules Prescribing Information (PI) received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on November 27, 2019.
- Approved PROCYSBI delayed-release oral capsules, for oral use comparator labeling dated May 31, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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MARCIA B WILLIAMS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 14, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213491
Product Name and Strength:	Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg and 300 mg
Applicant/Sponsor Name:	Horizon Pharma USA, Inc
OSE RCM #:	2019-1094-1
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 12, 2019 for Procysbi delayed-release oral granules. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container labels and carton labeling for Procysbi delayed-release oral granules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Owens, L. Label and Labeling Review for Procysbi delayed-release oral granules (NDA 213491). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 11. RCM No.: 2019-1094.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 12, 2019

Container labels

(b) (4)

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 11, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 213491
Product Name and Strength:	Procysbi (cysteamine bitartrate) delayed-release oral granules, 75 mg and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Horizon Pharma USA, Inc.
FDA Received Date:	May 16, 2019
OSE RCM #:	2019-1094
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Procysbi (cysteamine bitartrate) delayed-release oral granules, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Procysbi prescribing information (PI), container labels, carton labeling, medication guide, and instructions for use for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 213491 is a 505(b)(2) NDA and the listed drug product is Procysbi Capsules, NDA 203389.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 below include the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Horizon Pharma USA, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The NDC number (b) (4) (b) (4)	(b) (4)	Revise the middle NDC digits. However, if for some reason the middle digits cannot be revised, increase the prominence of the

Table 2. Identified Issues and Recommendations for Horizon Pharma USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4) The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. (b) (4) [redacted]	middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-XXXX-XX
2.	The NDC number is not located on the principal display panel (PDP).	Lack of inclusion of the NDC on the PDP may lead to selection errors, as the NDC number is used as an additional check when dispensing drug products.	Add the NDC number to the top of the principal display panel (PDP).
3.	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Table 2. Identified Issues and Recommendations for Horizon Pharma USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The proprietary name and established names lack prominence on primary display panel (PDP).	The proprietary and established names may be overlooked and/or misinterpreted leading to potential medication errors.	Increase the prominence of the proprietary and established names. Ensure that the established name is at least ½ the size of the proprietary name and in accordance with 21 CFR 201.10(g)(2).
5.	As currently presented the lot number is omitted.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit (usually the carton) display a human-readable and machine-readable (2D data matrix barcode) product identifier. Ensure the lot number is clearly differentiated from the expiration date on the label.
Carton Labeling			
1.	The usual dose statement on the carton is currently presented as: (b) (4)	The usual dosage statement should meet 21 CFR 201.55 and maintain consistency with the Prescribing Information	Revise the Usual Dosage statement to read: "Recommended Dosage: See prescribing information"
2.	The (b) (4) statement is currently located on the principal display panel (PDP)	As currently presented, this statement adds clutter to the PDP and may minimize important information	Relocate the statement: (b) (4) to the side panel

5 CONCLUSION

Our evaluation of the proposed Procysbi container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations for the Applicant. We ask that the Division convey Table 2 in its entirety to Horizon Pharma USA, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Procysbi that Horizon Pharma USA, Inc. submitted on May 16, 2019, and the listed drug (LD).

Table 3. Relevant Product Information for Listed Drug and Procysbi

Product Name	Procysbi	Procysbi
Initial Approval Date	April 30, 2013	N/A
Active Ingredient	Cysteamine Bitartrate	
Indication	treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older	
Route of Administration	Oral	
Dosage Form	Delayed-release Capsule	Delayed-release Granule
Strength	25 mg and 75 mg	75 mg and 300 mg
Dose and Frequency	<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>	
How Supplied	• 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 • 75 mg cysteamine: A hard gelatin capsule with dark blue opaque cap imprinted with “PRO” in white ink	• 75 mg cysteamine: (b) (4) containing white to off-white granules, supplied as 60 packets in a carton • 75 mg cysteamine: (b) (4) containing white to off-white granules, supplied as 120 packets in a carton • 300 mg cysteamine: (b) (4) containing white to off-white granules,

	and light blue opaque body imprinted with “75 mg” in white ink, supplied as bottle of 250 capsules	supplied as 60 packets in a carton • 300 mg cysteamine: (b) (4) containing white to off-white granules, supplied as 120 packets in a carton
Storage	(b) (4)	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Procysbi labels and labeling submitted by Horizon Pharma USA, Inc..

- Container label(s) received on May 16, 2019
- Carton labeling received on May 16, 2019
- Instructions for Use (Image not shown) received on May 16, 2019
- Prescribing Information (Image not shown) received on May 16, 2019

F.2 Label and Labeling Images

Container label(s)

(b) (4)

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

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