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Pediatric Postmarketing Pharmacovigilance Review

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Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Procysbi (cysteamine bitartrate)	December 22, 2017	NDA 203389 NDA 213491	Horizon
Cystadrops (cysteamine ophthalmic solution)	August 19, 2020	NDA 211302	Recordati Rare

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Procysbi (cysteamine bitartrate) and Cystadrops (cysteamine ophthalmic solution) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) for Procysbi and the Pediatric Research Equity Act (PREA) for Cystadrops. This review focuses on U.S. serious unlabeled adverse events associated with cysteamine in pediatric patients.

Procysbi was first approved by FDA on April 30, 2013, for the management of nephropathic cystinosis in patients 6 years and older. On August 14, 2015, FDA extended the indication for Procysbi to include patients aged 2 years and older. On December 22, 2017, FDA again expanded the indication for Procysbi to include use in patients 1 year and older. The safety and effectiveness of Procysbi have not been established in patients less than 1 year of age. Cystadrops was approved by FDA on August 19, 2020, for the treatment of corneal cystine crystal deposits in adults and children with cystinosis. This pediatric postmarketing pharmacovigilance review was prompted by pediatric labeling change for Procysbi on December 22, 2017, and the approval of Cystadrops on August 19, 2020.

DPV reviewed all U.S. serious FAERS reports for cysteamine in the pediatric population (ages 0 <17 years) from August 17, 2017, through August 31, 2022. The FAERS search identified 40 U.S. serious reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to cysteamine.

DPV will continue to monitor all adverse events associated with the use of cysteamine.

Reference ID: 5055457

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Procysbi (cysteamine bitartrate) and Cystadrops (cysteamine ophthalmic solution) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) for Procysbi and the Pediatric Research Equity Act (PREA) for Cystadrops. This review focuses on U.S. serious unlabeled adverse events associated with cysteamine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Procysbi (NDA 203389) is an oral, delayed-release capsule cystine-depleting agent first approved by FDA on April 30, 2013, for the management of nephropathic cystinosis in patients 6 years and older. On August 14, 2015, FDA extended the indication for Procysbi to include patients aged 2 years and older. On December 22, 2017, FDA again expanded the indication for Procysbi to include use in patients 1 year and older. Evidence of safety and effectiveness of Procysbi in this pediatric age group relied on an open-label trial in 15 cysteamine treatment-naive pediatric patients 1 year to less than 6 years of age (Study RP103-08). The study assessed the effectiveness of Procysbi in reduction of white blood cell cystine levels and in improvement of body weight and standing height. The safety and effectiveness of Procysbi have not been established in patients less than 1 year of age. A summary of the study design and findings are summarized below from the Procysbi Clinical Review.[1]

> "A total of 15 pediatric patients age <6 years were enrolled. Fourteen of them completed 12-month treatment, and 10 of the 14 continued to complete 18-month treatment. The results show that the mean cystine level was numerically decreased from 3.1 nmol ½ cystine/mg protein on Day 1 to 0.80 nmol at Month 12 of Procysbi treatment. Responder analysis shows that the proportion of subjects who had low WBC cystine levels (<1.0 nmol ½ cystine/mg protein) increased from 20.0% on Day 1 to 76.9% at Study Exit (Note: There were 10 subjects who completed 18-month study and 3 subjects who completed 12-month study). The chronic renal disease was stabilized as demonstrated by the increase of estimated GFR from 55 mL/min/1.73 m^2 at baseline to 63 mL/min/1.73 m^2 at Study Exit.
>
> The clinical data show that the mean height increased from 2.5 percentile on Day 1 to 50.5 percentile at Study Exit. The mean Z-scores of heights increased from -3.1 (Day 1) to 0.1 (Study Exit). The mean weight increased from 3.4 percentile on Day 1 to 32.8 percentile at Study Exit. The mean Z-scores of weights increased from -3.9 (Day 1) to -1.1 (Study Exit).
>
> Safety assessment of Study RP103-08 (15 Procysbi-treatment naïve patients) shows one death (1/15, 6%) due to gastroenteritis, vomiting, and hypovolemic shock. There were 4 patients (4/15, 26%) who had vomiting defined as serious adverse events (SAEs, non-fatal). The most common adverse events (AEs) were vomiting (8/15, 53%), gastroenteritis (5/15, 33%), and diarrhea (3/15, 20%)."

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Procysbi (NDA 213491) is also available as an oral, delayed-release granule packet approved by the FDA on February 14, 2020.[2]

Cystadrops (NDA 211302) is an ophthalmic solution approved by FDA on August 19, 2020, for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.[3] A summary of the study design and findings are summarized below from the Cystadrops Summary Review for Regulatory Action.[4]

> "The data contained in this submission establishes the efficacy of CYSTADROPS (cysteamine ophthalmic solution) 0.37% dosed qid to decrease corneal cystine crystal deposits in adults and children with cystinosis. Reductions in crystal deposits (crystals) is associated with decreased ocular symptoms.
>
> Studies OCT-1 and CHOC demonstrate ability of CYSTADROPS to decrease corneal cystine crystal deposits. In Study OCT-1, the absolute mean number of crystals observed by In Vivo Confocal Microscopy (IVCM) from baseline was clinically reduced from month 6 through month 60. In Study CHOC, the absolute decrease from baseline in crystals observed by IVCM was clinically reduced at month 3.
>
> The most common ocular adverse events after treatment with CYSTADROPS (incidence approximately 10% or greater) were: eye pain, vision blurred, eye irritation, ocular hyperemia, eye pruritus, lacrimation increased, deposit eye, and instillation site discomfort. Most of these events are also associated with the disease being treated.
>
> The benefit of CYSTADROPS (cysteamine ophthalmic solution) 0.37% in decreasing corneal cystine crystal deposits outweighs the minimal risks to patients with Cystinosis."

This pediatric postmarketing pharmacovigilance review was prompted by pediatric labeling change for Procysbi on December 22, 2017, and the approval of Cystadrops on August 19, 2020. DPV previously evaluated postmarketing adverse event reports with a serious outcome for Procysbi in pediatric patients. DPV's evaluation, dated April 4, 2018, was prompted by the pediatric labeling change on August 14, 2015.[5] DPV's evaluation did not identify any new safety concerns and resulted in recommendations to return to routine monitoring for adverse events with Procysbi. Of note, DPV has not previously presented Cystadrops to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

1.2.1 Procysbi

The Procysbi labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[2] For further labeling information, please refer to the full prescribing information.

----------CONTRAINDICATIONS----------

Hypersensitivity to penicillamine or cysteamine (4)

----------WARNINGS AND PRECAUTIONS----------

- Ehlers-Danlos-like Syndrome: Reduce dosage if skin and bone lesions occur. (5.1)
- Skin Rash: Discontinue if severe skin rash such as erythema multiforme bullosa or toxic epidermal necrolysis occurs. (5.2)
- Gastrointestinal (GI) Ulcers and Bleeding: Monitor for GI symptoms and consider decreasing the dose if severe symptoms occur. (5.3)
- Fibrosing Colonopathy: Evaluate patients with severe, persistent, and/or worsening abdominal symptoms for fibrosing colonopathy. If the diagnosis is confirmed, permanently discontinue PROCYSBI and switch to immediate-release cysteamine bitartrate capsules (5.4)
- Central Nervous System (CNS) Symptoms: Monitor for CNS symptoms; interrupt or reduce the dose for severe symptoms or those that persist or progress (5.5).
- Leukopenia and/or Elevated Alkaline Phosphatase Levels: Monitor white blood cell count and alkaline phosphatase levels; decrease or discontinue the dose until values revert to normal. (5.6)
- Benign Intracranial Hypertension: Monitor for signs and symptoms; interrupt or reduce the dose for signs/symptoms that persist, or discontinue if diagnosis is confirmed. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions in:

- Patients 6 years of age and older previously treated with cysteamine (≥5%) are: vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash, and headache. (6.1)
- Patients 1 year to less than 6 years naïve to cysteamine treatment (>10%) are: vomiting, gastroenteritis/viral gastroenteritis, diarrhea, breath odor, nausea, electrolyte imbalance and headache. (6.1)

8.4 Pediatric Use

The safety and effectiveness of PROCYSBI have been established in pediatric patients 1 year of age and older for the treatment of nephropathic cystinosis. Use of PROCYSBI is supported by evidence from patients switched to PROCYSBI from immediate-release cysteamine bitartrate in two trials: an open-label, randomized, cross-over trial in adults and pediatric patients aged 6 years and older (n=43) and an open-label extension trial in pediatric patients aged 2 years and older (n=59). Another open-label trial was conducted in cysteamine naïve pediatric patients 1 year to less than 6 years of age (n=15) *[see Clinical Trials (14.2)]*. The safety profile in pediatric patients was similar to adults. In patients less than 6 years of age, vomiting occurred in 12/15 cysteamine treatment naïve patients compared to 11/13 patients switched from immediate-release cysteamine to PROCYSBI.

The safety and effectiveness of PROCYSBI have not been established in patients less than 1 year of age.

1.2.2 Cystadrops

The Cystadrops labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[3] For further labeling information, please refer to the full prescribing information.

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

To minimize the risk of contamination, do not touch the dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 10%) are eye pain, vision blurred, eye irritation, ocular hyperaemia, instillation site discomfort, eye pruritus, lacrimation increased, and ocular deposits. (6)

8.4 Pediatric Use

The safety and effectiveness of CYSTADROPS has been established in pediatric patients. Use of CYSTADROPS is supported by adequate and well controlled trials in pediatric patients and additional experience supporting the safety of CYSTADROPS.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1.**

Table 1. FAERS Search Strategy*	
Date of search	September 1, 2022
Time period of search	August 17, 2017† - August 31, 2022
Search type	RxLogix PV Reports Quick Query
Product Terms	Active Ingredient: cysteamine; cysteamine bitartrate; cysteamine hydrochloride
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. † The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for cysteamine bitartrate ended on August 16, 2017. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

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3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from August 17, 2017, through August 31, 2022, with cysteamine.

Table 2. Adult and Pediatric FAERS Reports* Received by FDA from August 17, 2017, through August 31, 2022 with Cysteamine

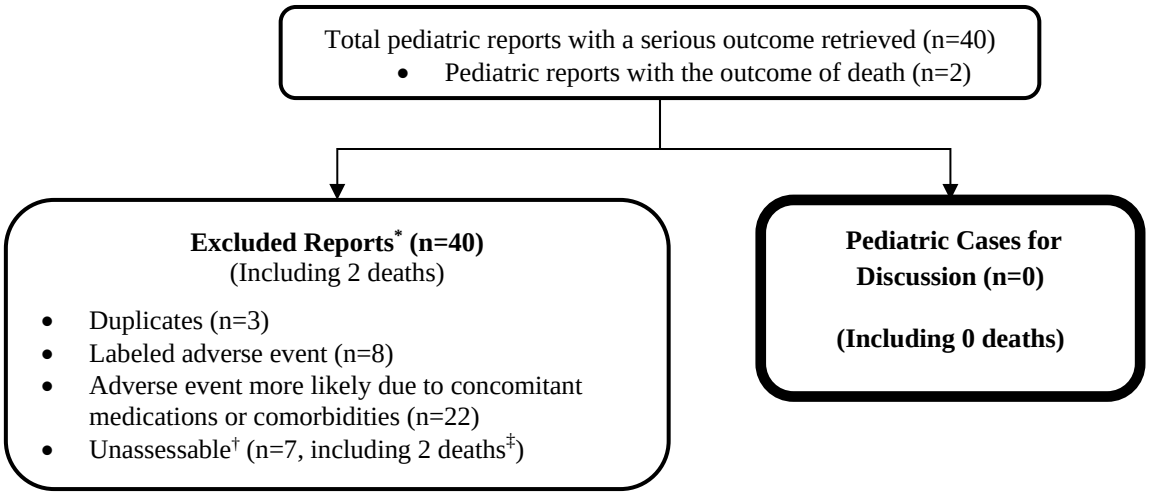
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	189 (147)	112 (71)	14 (11)
Pediatrics (0 - <17 years)	148 (116)‡	72 (40)‡	11 (2)‡

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. One additional report of pediatric death was identified among reports not reporting an age.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 40 U.S. serious pediatric reports from August 17, 2017, through August 31, 2022. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all reports from the case series for various reasons such as adverse event more likely due to concomitant medications or comorbidites (n=22), labeled adverse event (n=8), unassessable reports (n=7), or duplicate reports (n=2). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Cysteamine



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above
† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.
‡ Two reports described fatal outcomes. Both reports indicated a patient died but provided no other clinical detail.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion with cysteamine.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any unlabeled non-fatal adverse event cases associated with cysteamine in the pediatric population.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports for cysteamine in the pediatric population (ages 0 <17 years) from August 17, 2017, through August 31, 2022. During this time, the majority of FAERS reports described adverse events that were more likely due to concomitant medications or comorbidities, or were consistent with labeled events described in the cysteamine labeling. We did not identify an increase in severity in the labeled adverse events.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for cysteamine at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of cysteamine.

7 REFERENCES

1. Gao W-Y. Medical Officer Review of Procysbi (cysteamine bitartrate) delayed release capsules. December 2017. https://www.fda.gov/media/110986/download.
2. Procysbi®(cysteamine bitartrate) delayed-release capsules, for oral use [Prescribing Information]. Deerfield, IL: Horizon Therapeutics USA, Inc.; February 2022.
3. Cystadrops®(cysteamine hydrochloride) ophthalmic solution/drops [Prescribing Information]. Lebanon, NJ: Recordati Rare Disease Inc.; August 2020.
4. Chambers W. Summary Review for Regulatory Action of Cystadrops®(cysteamine hydrochloride). December 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211302Orig1s000SumR.pdf.
5. Kim I, Harinstein L, Muñoz M, Chai G. FDA Office of Surveillance and Epidemiology - Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review- Procysbi (cysteamine bitartrate). 2015. https://www.fda.gov/media/113582/download.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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