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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name(s):	Procysbi (cysteamine bitartrate)
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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for cysteamine bitartrate products, Procysbi and Cystagon, in pediatric patients. This review was triggered by the pediatric labeling date for Procysbi.

Procysbi is a delayed-release cysteamine bitartrate product first approved in 2013 for the treatment of nephropathic cystinosis in patients aged 6 years and older. The indication for Procysbi was extended in 2015 to include patients 2 years and older and most recently in 2017 to include patients aged 1 year and older. Procysbi was approved under a 505(b)(2) regulatory pathway that relied upon the safety and effectiveness of the reference listed drug (RLD), Cystagon (cysteamine bitartrate/ NDA 020392). Cystagon is an immediate-release formulation of cysteamine bitartrate approved in 1994 for the treatment of nephropathic cystinosis in adults and children.

For the purposes of this review, we searched the FDA Adverse Event Reporting System (FAERS) database for all the reports of adverse events with cysteamine bitartrate, which included reports for both Procysbi and Cystagon, from September 1, 2015 through August 16, 2017. The review of the FAERS pediatric reports resulted in the identification of eight foreign pediatric cases with the serious outcome of death. All the death cases involved an unspecified cysteamine bitartrate formulation.

Of the eight foreign death cases, six did not contain sufficient information to determine the patient's cause of death; five of the six were reported from one literature article characterizing the clinical course of cystinosis and the sixth case derived from a literature article discussing the ophthalmologic findings of a child with cystinosis. The remaining two death cases described infection (pneumonia and an unspecified infection) as the cause of death; the limited number of cases do not provide enough clinical details to determine if cysteamine bitartrate contributed to the fatal events.

The pediatric safety profile described in most FAERS cases is consistent with the known safety profile and the current cysteamine bitartrate label. No new safety signal was identified with cysteamine bitartrate. OSE plans to continue postmarketing surveillance of all adverse events with the use of cysteamine bitartrate in pediatric patients.

1 INTRODUCTION

This review evaluated pediatric postmarketing adverse event reports with a serious outcome for two cysteamine bitartrate products, Procysbi and Cystagon, contained in the FDA Adverse Event Reporting System (FAERS) database. This review was triggered by the pediatric labeling date for Procysbi.

1.1 PRODUCT FORMULATION AND INDICATION

Procysbi (cysteamine bitartrate/ NDA 203389) is an oral, delayed-release cystine-depleting agent approved by FDA on April 30, 2013 for the management of nephropathic cystinosis in adults and children ages 2 years and older. Procysbi was approved under a 505(b)(2) regulatory pathway that relied upon the safety and effectiveness of the reference listed drug (RLD), Cystagon (cysteamine bitartrate/ NDA 020392). Cystagon is an oral, immediate-release cystine-depleting agent approved on August 15, 1994 for the management of nephropathic cystinosis in children and adults.[1, 2] Procysbi and Cystagon are differentiated from each other by the indicated ages for use, dosage forms, and dosing interval (see Table 1).

Table 1. FDA Approved Cysteamine Bitartrate Products and Approval Information

Proprietary name	*NDA*	*Original approval date*	*Dosage form*	*Dosage interval*	*Current approved population*
Procysbi	203389	04/30/2013	25 mg, 75 mg delayed-release capsules	Every 12 hours	Adults and pediatric patients 1 year of age and older
Cystagon	020392	08/15/1994	50 mg, 150 mg immediate-release capsules	Every 6 hours	Adults and children

Cystinosis is a rare autosomal recessive disorder with an incidence of 1:100,000 to 200,000 live births. It is characterized by the abnormal transport of cysteine out of cellular lysosomes due to mutations in the *CTNS* gene. Clinical features include renal Fanconi syndrome, rickets, growth failure, hypothyroidism, delayed puberty, ocular disease, and central nervous system disease. The nephropathic form of cystinosis is a multisystem disease and accounts for approximately 95% of cystinosis cases. Without treatment, the natural history of cystinosis results in death due to renal failure in children under the age of ten years.[3]

Cysteamine bitartrate is an aminothiol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with cystinosis. White blood cell (WBC) cystine concentration is the accepted biomarker for cystine depletion and is used for therapeutic monitoring of cysteamine bitartrate products. Cysteamine treatment is not curative, but slows progression of cystinosis, enhances growth, prevents several of the non-renal complications, and increases survival to beyond 50 years of age with renal replacement therapy.[4]

1.2 PEDIATRIC REGULATORY HISTORY

August 15, 1994: Cystagon (NDA 020392) gained FDA approval for the management of nephropathic cystinosis in children and adults.

June 06, 2007: Cystagon supplemental NDA (sNDA) 020392/S-010 was approved, which provided revisions in the Precautions and Adverse Reactions sections of labeling regarding benign intracranial hypertension and serious skin lesions. The updated labeling included reports of serious skin lesions in patients treated with high doses of cysteamine bitartrate or other cysteamine salts; the lesions include molluscoid pseudotumor lesions on elbows and striae in different locations on the body.

April 30, 2013: Procysbi (NDA 203389) obtained initial FDA approval for treatment of nephropathic cystinosis in adults and children ages 6 years and older. Procysbi was approved under the 505(b)(2) regulatory pathway, which relied on proprietary safety and efficacy data of the RLD, Cystagon (NDA 020392). The data for approval came from Study RP103-03.[5, a] This was a 9-week randomized, cross-over, non-inferiority clinical trial comparing delayed-release cysteamine bitartrate to immediate-release cysteamine bitartrate with respect to depletion of WBC cystine concentrations. Procysbi was exempt from Pediatric Research Equity Act (PREA) obligations due to its orphan drug designation.

August 14, 2015: FDA approved Procysbi sNDA 203389/S-010 that expanded the indication to adults and children ages 2 years and older. Data to support S-010 was derived from study RP103-04,[6, b] which was an extension of RP103-03; the study included an additional 13 patients aged 2 to 6 years who took Cystagon and switched to Procysbi for 12 months. The postmarketing safety of Procysbi was also evaluated during review of this supplement. The Division of Gastroenterology and Inborn Errors Products (DGIEP) assessed all 15-day reports from the FAERS database from July 2013 to August 2015 and Procysbi Periodic Adverse Drug Experience Reports covering the period of July 2013 to April 2015. Most reported events were consistent with known Procysbi adverse events. Unexpected adverse events included musculoskeletal pain, neuropsychiatric and neuromuscular symptoms, renal impairment or disease, and gastronomy tube occlusion. In most of these cases, complications from underlying cystinosis could not be excluded or the patients had other underlying conditions diagnosed prior to cysteamine initiation that could explain the adverse events. DGIEP concluded that the information was supportive of the overall conclusion that the safety profile of Procysbi is similar to other cysteamine products and is consistent with the updated safety information in the product labeling.[7]

June 29, 2017: The Sponsor of Procysbi submitted sNDA 203389/S-020 to propose extending the indication of Procysbi to patients less than 2 years old. Additionally, the Sponsor requested the determination of pediatric exclusivity based on Study RP103-08,[8, c] an open-label pharmacokinetic, pharmacodynamic, safety, and efficacy study in pediatric patients with nephropathic cystinosis aged birth to less than 6 years. The results for treatment naïve patients less

[a] Retrieved from https://clinicaltrials.gov (Identification No. NCT01000961)
[b] Retrieved from https://clinicaltrials.gov (Identification No. NCT01197378)
[c] Retrieved from https://clinicaltrials.gov (Identification No. NCT01744782)

than 6 years old were comparable to those in patients aged 6 years and older from previous studies RP103-03 and RP 103-04.[9] No patients under 1 year of age were enrolled in RP103-08.

December 22, 2017: FDA approved Procysbi sNDA 203389/S-020 to expand the indication for Procysbi for the treatment of nephropathic cystinosis in treatment naïve patients age 1 year and older.[10] The submission also contained the final study report for the RP103-08 study to fulfill the pediatric WR and granted pediatric exclusivity for Procysbi.[9,11]

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

Select safety information from the Procysbi product label dated December 2017 is included below:

5 WARNINGS AND PRECAUTIONS

5.1 Ehlers-Danlos-like Syndrome
Skin and bone lesions that resemble clinical findings for Ehlers-Danlos-like syndrome have been reported in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts. These include molluscoid pseudotumors (purplish hemorrhagic lesions), skin striae, bone lesions (including osteopenia, compression fractures, scoliosis and genu valgum), leg pain, and joint hyperextension. One patient on immediate-release cysteamine bitartrate with serious skin lesions subsequently died of acute cerebral ischemia with marked vasculopathy. Monitor patients for development of skin or bone lesions and interrupt PROCYSBI dosing if patients develop these lesions. PROCYSBI may be restarted at a lower dose under close supervision, then slowly increase to the appropriate therapeutic dose *[see Dosage and Administration (2.1, 2.4)]*.

5.2 Skin Rash
Severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. If severe skin rashes develop, permanently discontinue use of PROCYSBI *[see Contraindications (4)]*.

5.3 Gastrointestinal Ulcers and Bleeding
Gastrointestinal (GI) ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. GI tract symptoms including nausea, vomiting, anorexia and abdominal pain, sometimes severe, have been associated with cysteamine. If severe GI tract symptoms develop, consider decreasing the dose of PROCYSBI *[see Dosage and Administration (2.2)]*.

5.4 Central Nervous System Symptoms
Central Nervous System (CNS) symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine. Neurological complications have also been described in some patients with cystinosis who have not been treated with cysteamine. Carefully evaluate and monitor patients who develop CNS symptoms. Interrupt medication or adjust the dose as necessary for patients with severe symptoms or with symptoms that persist or progress. Inform patients that PROCYSBI may impair their ability to perform tasks such as driving or operating machinery.

5.5 Leukopenia and/or Elevated Alkaline Phosphatase Levels
Cysteamine has been associated with reversible leukopenia and elevated alkaline phosphatase levels. Monitor white blood cell counts and alkaline phosphatase levels. If tests values remain elevated, consider decreasing the dose or discontinuing the drug until values revert to normal.

5.6 Benign Intracranial Hypertension
Benign intracranial hypertension (pseudotumor cerebri; PTC) and/or papilledema have been reported in patients receiving immediate-release cysteamine bitartrate treatment. Monitor patients for signs and symptoms of PTC, including headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye or pain with eye movement. If signs/symptoms persist, interrupt dosing or decrease the dose and refer the patient to an ophthalmologist. If the diagnosis is confirmed, permanently discontinue use of PROCYSBI.

6.2 Postmarketing Experience

Musculoskeletal: Joint hyperextension, leg pain, osteopenia, compression fracture, scoliosis, genu valgum *[see Warnings and Precautions (5.1)]*

Skin: Erythema multiforme bullosa, toxic epidermal necrolysis, Ehlers-Danlos-like syndrome, molluscoid pseudotumors, skin striae, skin fragility *[see Warnings and Precautions (5.1, 5.2)]*.

Central Nervous System: seizures, lethargy, somnolence, depression, and encephalopathy *[see Warnings and Precautions (5.4)]*, benign intracranial hypertension (or PTC) and/or papilledema *[see Warnings and Precautions (5.6)]*.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

The Division of Pharmacovigilance I (DPV-I) searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	August 16, 2017
Time Period of Search	September 1, 2015* through August 16, 2017
Search Type	Product-Manufacturer Reporting Summary Quick Query
Product Active Ingredient	Cysteamine Cysteamine bitartrate
Search Parameters	All ages, all outcomes, worldwide

** The pediatric postmarketing safety of Procysbi from July 2013 to August 2015 was previously reviewed by DGIEP as part of the review of sNDA 203389/S-010. Therefore, the data lock date of August 2015 was used to inform the start date of this review.[10]*

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* from September 1, 2015 through August 16, 2017 with Cysteamine Bitartrate

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	109 (95)	70 (56)	10 (10)
Pediatrics (0 - <17 years)	111 (95)	**43‡ (28)**	8 (0)

** May include duplicates and transplacental exposures, and have not been assessed for causality*

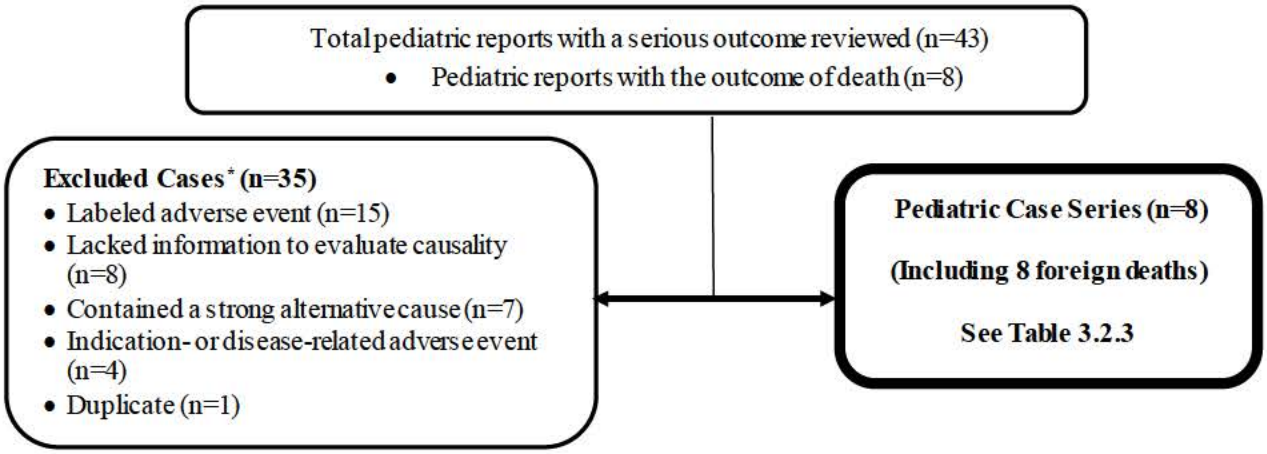
† For the purposes of this review, the following outcomes qualify as serious: death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 43 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Section 3.3.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Cysteamine Bitartrate



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

We identified 43 pediatric reports with serious outcomes, of which one was a duplicate. Of the remaining 42 reports, 15 described labeled adverse events; the labeled events included vomiting (n=9), benign intracranial hypertension (n=2), nausea (n=1), abdominal ulcer (n=1), abdominal pain (n=1), and skin lesions (n=1). Ten of the 15 labeled event reports resulted in hospitalization. Reasons for hospitalization included dehydration (n=7), complications from labeled events including infection and electrolyte imbalance (n=2), and planned admission for a feeding program (n=1). No change was noted in the frequency or severity of the labeled adverse events.

Eight serious pediatric reports lacked information to establish causality. The reports generally stated that a patient experienced a serious adverse event, including renal dysfunction (n=3), anxiety (n=1), pleural fluid (n=1), dehydration (n=1), seizure (n=1), and hospitalization due to unspecified cause (n=1), but offered no additional history or details regarding temporality, dechallenge, or rechallenge.

Seven serious pediatric reports described strong alternative causes for the adverse event. Strong alternative causes included rotavirus, streptococcus pharyngitis, and otitis media infections that led to dehydration and hospitalization (n=2); other conditions and procedures that required hospitalization for monitoring (n=2; constipation leading to ileus, scheduled tonsillectomy with myringotomy tube insertion); parent inexperience with gastrostomy tube medication administration technique (n=1) that led to device occlusion; accidental overdose that caused vomiting (n=1); and child medical neglect that led to hospitalization (n=1).

Four serious pediatric reports contained adverse events that were deemed to be related to the patient's underlying disease. The patients in the four reports underwent surgeries to address complications from cystinosis progression; these included renal transplant for renal failure (n=2), spinal fusion for progression of scoliosis (n=1), and g-tube placement for medication administration and nutrition (n=1). The remaining eight cases are discussed below.

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Cysteamine Bitartrate (N=8)

Age (n=7)	2 - < 6 years	4
	6 - <12 years	3
Sex (n=7)	Female	3
	Female	4
Country	Foreign	8
Serious Outcome*	Death	8
	Hospitalized	1
	Other serious	2

** For the purposes of this review, the following outcomes qualify as serious: death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.*

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=8)

There were eight foreign pediatric cases with an outcome of death reported with cysteamine use in the FAERS database from September 1, 2015 through August 16, 2017. All of the cases involved an unspecified cysteamine bitartrate formulation. Of the eight death cases, six did not contain sufficient information to determine the patient's cause of death; five of the six were reported from one literature article characterizing the clinical course of cystinosis[12] and the sixth case, derived from a medical literature article, discussed the ophthalmologic findings of a child with cystinosis.[13] None of the six cases offered additional patient-level detail for causation analysis. The remaining two cases originated from the medical literature and described infection as the cause of death: one case described an infant who developed an unspecified infection[14] and the remaining case involved a child of unspecified age who had inconsistent cysteamine treatment due to familial neglect and later developed a pulmonary infection.[15]

Reviewer comment: Leukopenia is labeled within Warnings and Precautions Section 5.5 of the Procysbi product label and may suggest a mechanism for the development of infection. The limited number of cases do not provide enough clinical details to determine what role, if any, cysteamine bitartrate contributed to the fatal events. None of the cases reported laboratory information to determine if leukopenia was present at the time of the infection. Notably, two of the literature articles that describe six of the death cases refer to a lack of technical and financial resources that may hinder early diagnosis and treatment of cystinosis. There were no U.S. cases of death with cysteamine bitartrate identified, which suggests that differences in medical practice standards, resources, and access to care may contribute to severity of underlying cystinosis and to the outcome of death.[17,20]

3 DISCUSSION

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for cysteamine bitartrate (Procysbi and Cystagon) in the FAERS database from September 1, 2015 through August 16, 2017. We identified eight foreign pediatric cases with an outcome of death. Of the eight death cases, six did not contain sufficient information to determine the patient's cause of death and two died from infection; the two cases with an infectious cause of death contained insufficient information to determine if cysteamine bitartrate was contributory to the fatal event. There were no new safety signals identified for cysteamine bitartrate. We recommend continued pharmacovigilance of all adverse events with cysteamine bitartrate at this time.

4 CONCLUSION

DPV-I analyzed all pediatric postmarketing adverse event reports with a serious outcome for cysteamine bitartrate in the FAERS database from September 1, 2015 through August 16, 2017. There is no evidence of pediatric safety concerns with cysteamine bitartrate that warrant a labeling update at this time.

5 RECOMMENDATIONS

OSE recommends returning to routine pharmacovigilance monitoring for all adverse events with cysteamine bitartrate.

6 APPENDICES

6.1 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 events and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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 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 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.

6.2 APPENDIX B FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH CYSTEAMINE BITARTRATE (N=10)

FAERS Case	*Version Number*	*Manufacturer Control Number*
11941935	1	BR-MYLANLABS-2016M1003411
13076126	1	TR-MYLANLABS-2016M1057286
13114775	1	IN-MYLANLABS-2017M1001993
13114780	1	IN-MYLANLABS-2017M1001996
13114791	1	IN-MYLANLABS-2017M1001998
13114961	1	IN-MYLANLABS-2017M1002000
13115013	1	IN-MYLANLABS-2017M1001747
13551709	1	PT-MYLANLABS-2017M1029449

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