Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 1, 2018
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Product Name(s):	Pancreaze (pancrelipase) Pertzye (pancrelipase)
Pediatric Labeling Approval Date:	March 7, 2014 (Pancreaze) October 6, 2016 (Pancreaze)
Application Type/Number:	NDA 022523/004 (Pancreaze) NDA 022175/003 (Pertzye)
Applicant/Sponsor:	Janssen Pharms (Pancreaze) Digestive Care Inc (Pertzye)
OSE RCM #:	2018-1221

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for two pancrelipase-containing pancreatic enzyme products (PEPs), Pancreaze (pancrelipase) and Pertzye (pancrelipase), in pediatric patients.

Pancreaze and Pertzye are porcine-derived PEPs consisting of pancrelipase, which contains lipases, proteases, and amylases. Pancreaze and Pertzye are indicated for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF) or other conditions in infants, children, and adults. There are currently four other PEPs available in the United States that are not interchangeable. On April 12, 2010, four formulations of Pancreaze (NDA 022523) were approved by FDA for use in infants, children, and adults; on March 7, 2014, a new formulation of Pancreaze (Capsules: 2,600 USP units of lipase; 6,200 USP units of protease; 10,850 USP units of amylase) was approved by FDA to allow for dosing in infants up to 12 months of age. On May 16, 2012, two formulations of Pertzye (NDA 022175) were approved by FDA for use in children older than 12 months and adults; on October 6, 2016, a new formulation of Pertzye (Capsules: 4,000 USP units of lipase; 14,375 USP units of protease; 15,125 USP units of amylase) was approved by FDA to allow for dosing in infants up to 12 months of age. The approvals of the two formulations of Pancreaze and Pertzye, which allowed for dosing in infants up to 12 months of age, prompted this review.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for pancrelipase-containing PEPs, including the products of interest Pancreaze and Pertzye, in the FAERS database from June 1, 2013 to May 31, 2018. This start date was chosen to capture all reports from the data lock date of a previous review of the pediatric safety of select PEPs, which reviewed adverse event reports through May 31, 2013. We retrieved 59 pediatric postmarketing reports, of which 3 were duplicates and 9 did not contain an adverse event associated with a PEP. Of the remaining 47 reports, 33 contained events that were related to the patients underlying EPI or CF, including 1 fatal report attributed to worsening pulmonary disease. There were nine reports with limited information, including three fatal reports that did not contain the patient's cause of death. Although unknown, it is possible that the patient's underlying CF was contributory to the three fatal cases with limited information.

Four reports contained labeled events for PEPs including gastrointestinal-related adverse events (n=3) and hypersensitivity (n=1). The reports are not unusual in number and no change in severity was noted from review of the reports. FDA required PEPs, which were initially regulated as dietary supplements, to be reviewed and approved NDAs after identifying the safety issue of fibrosing colonopathy. We did not identify any reports of fibrosing colonopathy in this review. We did identify one report of distal intestinal obstruction syndrome DIOS (n=1), which is labeled in the Adverse Reactions—Postmarketing Experience Section (6.2) of the PEPs labels,

but the case of DIOS was confounded by a concurrent diagnosis of appendicitis and ileus. Lastly, there was one report of a product physical issue with Creon.

The products of interest for this review were Pancreaze and Pertzye, although we evaluated all serious reports in pediatric patients with pancrelipase-containing PEPs for completeness. There were no reports in the FAERS database from June 1, 2013 to May 31, 2018 with Pancreaze and 10 reports associated with Pertzye use. Of the 10 reports with Pertzye, three did not contain an adverse event and one was a duplicate. The remaining six reports contained adverse events related to the patient's EPI or CF.

There is no evidence from these data that there are any pediatric safety concerns with the PEPs of interest in this review, Pancreaze and Pertzye, or any other PEP included in the review (Creon, Ultresa, Zenpep, Viokace). We recommended routine pharmacovigilance monitoring for all pancrelipase-containing PEPs.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome in pediatric patients for two pancrelipase-containing pancreatic enzyme products (PEPs), Pancreaze (pancrelipase) and Pertzye (pancrelipase).

1.1 FORMULATIONS AND INDICATIONS

Pancreaze[1] and Pertzye[2] are porcine-derived PEPs consisting of pancrelipase, which contains lipases, proteases, and amylases. Pancreaze and Pertzye are indicated for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF) or other conditions in infants, children, and adults. EPI clinically manifests as steatorrhea, abdominal pain, weight loss, and nutritional problems such as fat-soluble vitamin deficiencies because of malabsorption.[3] The administration of exogenous PEPs as a substitute for endogenous pancreatic enzymes is the mainstay of therapy for steatorrhea and malabsorption associated with EPI, regardless of the cause (e.g., CF, chronic pancreatitis).

There are currently six FDA approved pancrelipase-containing PEPs marketed in the United States that contain the same active ingredient, but are not interchangeable (see Table 1.1.1).

Table 1.1.1. FDA Approved Pancrelipase-Containing PEPs

Trade Name	Initial Approval	Formulation	Population for Use*
Creon	April 30, 2009	Delayed-release capsule	Infants, children, adults
Pancreaze†	April 12, 2010	Delayed-release capsule	Infants, children, adults
Pertzye†	May 17, 2012	Delayed-release capsule	Children, adults
Ultresa	March 1, 2012	Delayed-release capsule	Infants, children, adults
Viokace	March 1, 2012	Tablet	Adults
Zenpep	August 27, 2009	Delayed-release capsule	Infants, children, adults

* The infant population is age zero to 12 months of age and the children population are those older than 12 months of age.
† Products of interest for the current pediatric safety review

The dosing of the PEPs varies by product and patient age. The recommended dosage of Pancreaze in pediatric and adult patients is:[1]

- *Infants (up to 12 months):* 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.
- *Children older than 12 months and younger than 4 years:* Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.
- *Children 4 years and older and adults:* Enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

The recommended dosage of Pertzye in pediatric and adult patients is:[2]

- *Infants (up to 12 months):* 4,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding.
- *Children older than 12 months and younger than 4 years:* Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

- *Children 4 years and older and adults:* Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

1.2 PEDIATRIC REGULATORY HISTORY AND CLINICAL STUDIES[a]

Historically, animal-derived PEPs were regulated and marketed in the United States as dietary/nutritional supplements and were not regulated as new drugs under the new drug application (NDA) regulations. The products were considered to be generally recognized as safe and effective. FDA subsequently reconsidered the safety and effectiveness of animal-derived PEPs, in part based on reports of fibrosing colonopathy reported in the medical literature. On April 28, 2004, FDA announced that all PEPs are new drugs for which an NDA must be approved by April 28, 2008 for continued marketing (69 Federal Register [FR] 23410). In October 2007, FDA extended the date by which sponsors must have approved NDAs to April 28, 2010 (72 Federal Register 60860).

On April 12, 2010, Pancreaze (NDA 022523) was approved by FDA for the treatment of EPI due to CF or other conditions in infants, children, and adults in the following four formulations:

- Capsules: 4,200 USP units of lipase; 10,000 USP units of protease; 17,500 USP units of amylase
- Capsules: 10,500 USP units of lipase; 25,000 USP units of protease; 43,750 USP units of amylase
- Capsules: 16,800 USP units of lipase; 40,000 USP units of protease; 70,000 USP units of amylase
- Capsules: 21,000 USP units of lipase; 37,000 USP units of protease; 61,000 USP units of amylase

The safety and efficacy of Pancreaze in pediatric patients was assessed in two studies that included patients with CF-related EPI aged 6 to 30 months (Study 20-101)[4] and 7 to 18 years (Study PNCRLPCYS3001).[5] Safety and efficacy data from published literature and clinical experience with different formulations of pancrelipase (same active ingredient) was utilized to support approval of the use of Pancreaze in pediatric age groups not included in the two studies.[6] Two serious risks, fibrosing colonopathy and theoretical risk of transmission of porcine viral disease, were identified and included in a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide.[b]

Although, Pancreaze was approved in infants, a Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR 1629-1) was issued to submit a supplement for an age appropriate formulation in infants less than 12 months of age by October 2012 because the

[a] Regulatory history was adapted from the Medical Review in the Drug Approval Package for Pancreaze (available at: https://www.accessdata fda.gov/drugsatfda_docs/nda/2010/022523Orig1s000MedR.pdf) and Pertzye (available at: https://www.accessdata fda.gov/drugsatfda_docs/nda/2012/022175Orig1s000MedR.pdf)

[b] Two PMRs were issued at the time of approval: 1) a 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pancreaze in the US and to assess potential risk factors for the event (PMR 1629-2) and 2) a 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancreaze (PMR 1629-3).

available formulations did not allow for dosing in the youngest, lowest weight infants who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Pertzye was approved on May 16, 2012 by FDA for the treatment of EPI due to CF or other conditions in children older than 12 months and adults in the following two formulations:

- Capsules: 8,000 USP units of lipase; 28,750 USP units of protease; 30,250 USP units of amylase
- Capsules: 16,000 USP units of lipase; 57,500 USP units of protease; 60,500 USP units of amylase

The approval of Pertzye was based on one short-term randomized, double-blind, placebo-controlled, crossover study of 24 patients, ages 8 years to 43 years (Study 06-001).[7] The mean percent coefficient of fat absorption (CFA) was higher (statistically significant) with Pertzye treatment. Pertzye was not recommended for dosing in children >12 months and <4 years weighing < 8kg or children >4 years weighing <16 kg due to limitations on capsule dosage strengths. PMR 1894-1 was issued at the time of approval to develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or breast-feeding. The pediatric study requirement for ages birth to 1 months was waived because studies were deemed highly impracticable.

On March 7, 2014, a new formulation of Pancreaze (Capsules: 2,600 USP units of lipase; 6,200 USP units of protease; 10,850 USP units of amylase) was approved by FDA to allow for dosing in infants up to 12 months of age. This approval fulfilled PMR 1629-1.

On October 6, 2016, a new formulation of Pertzye (Capsules: 4,000 USP units of lipase; 14,375 USP units of protease; 15,125 USP unites of amylase) was approved by FDA, which fulfilled PMR 1894-1.

1.3 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

DPV-I evaluated all serious pediatric (0 to 16 years of age) postmarketing reports contained in the Adverse Event Reporting System (AERS) database with Creon, Zenpep, and Pancreaze from the approval date for each drug (see Table 1.1.1 for approval dates) to the data lock date of July 31, 2011 and found no major safety issues.[8] The Office of Pediatric Therapeutics (OPT) requested that DPV-I additionally focus on events of hyperuricemia, fibrosing colonopathy, and gastrointestinal (GI) obstruction; however no pediatric reports of these select adverse events of interest were identified.

Approval of an expanded indication for Creon and new lower strength dosage forms for Creon and Zenpep prompted a second review of pediatric postmarketing reports with these products.[9] DPV-I evaluated all serious pediatric (0 to 16 years of age) postmarketing reports contained in the FDA Adverse Event Reporting System (FAERS) database from July 31, 2011 to September 30, 2012 with Creon and Zenpep and found no new safety signals. Two reports of distal intestinal obstruction syndrome (DIOS) were identified, but were attributed to the patient's underlying disease.

Lastly, a review of serious and non-serious pediatric (0 to 17 years of age) postmarketing reports contained in the FAERS database from March 1, 2012 to May 31, 2013 with Ultresa and from May 17, 2012 to May 31, 2013 with Pertzye was completed.[10] No reports were found for these formulations of PEPs, thus no new safety issues were identified.

1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES

Pancreaze[1] and Pertzye[2] contain similar adverse events in their respective product labels. Select safety labeling pertinent to this review in the Pancreaze product label dated November 2013 is reproduced below.[1]

----------5 WARNINGS AND PRECAUTIONS----------

5.1 Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually with use over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in children less than 12 years of age. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day *[see Dosage and Administration (2.1)]*.

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat
absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

5.2 Potential for Irritation to Oral Mucosa

Care should be taken to ensure that no drug is retained in the mouth. PANCREAZE should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity *[see Dosage and Administration (2.2) and Patient Counseling Information (17)]*. For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce. The PANCREAZE-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

5.3 Potential for Risk of Hyperuricemia

Caution should be exercised when prescribing PANCREAZE to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

5.5 Allergic Reactions

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient

(pancrelipase). The risks and benefits of continued PANCREAZE treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

----------6 ADVERSE REACTIONS----------

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) include fibrosing colonopathy, hyperuricemia and allergic reactions *[see Warnings and Precautions (5)]*

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	May 17, 2018
Time Period of Search	June 1, 2013* - May 31, 2018
Search Type	Product-Manufacturer Reporting Summary Quick Query
Product Active Ingredient	pancrelipase amylase/ pancrelipase lipase/ pancrelipase protease†
Search Parameters	All ages, all outcomes, worldwide

** Multiple reviews of the pediatric safety of PEPs were previously presented to the Pediatric Advisory Committee (PAC). The most recent review completed October 29, 2013 reviewed the FAERS database through May 31, 2013. Therefore, this date was used to inform the start date of the search for this review.[10]*

† FAERS search strategy used Product Active Ingredient pancrelipase amylase/ pancrelipase lipase/ pancrelipase protease which retrieved reports with other pancrelipase products (Creon, Zenpep, Viokace, Ultresa) in addition to the product of interest, Pancreaze and Pertzye.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports* from June 1, 2013 to May 31, 2018 with Pancrelipase Amylase/ Pancrelipase Lipase/ Pancrelipase Protease

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1025 (904)	601 (486)	124 (112)
Pediatrics (0 - <17 years)	103 (91)	**59‡ (48)**	4 (3)

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

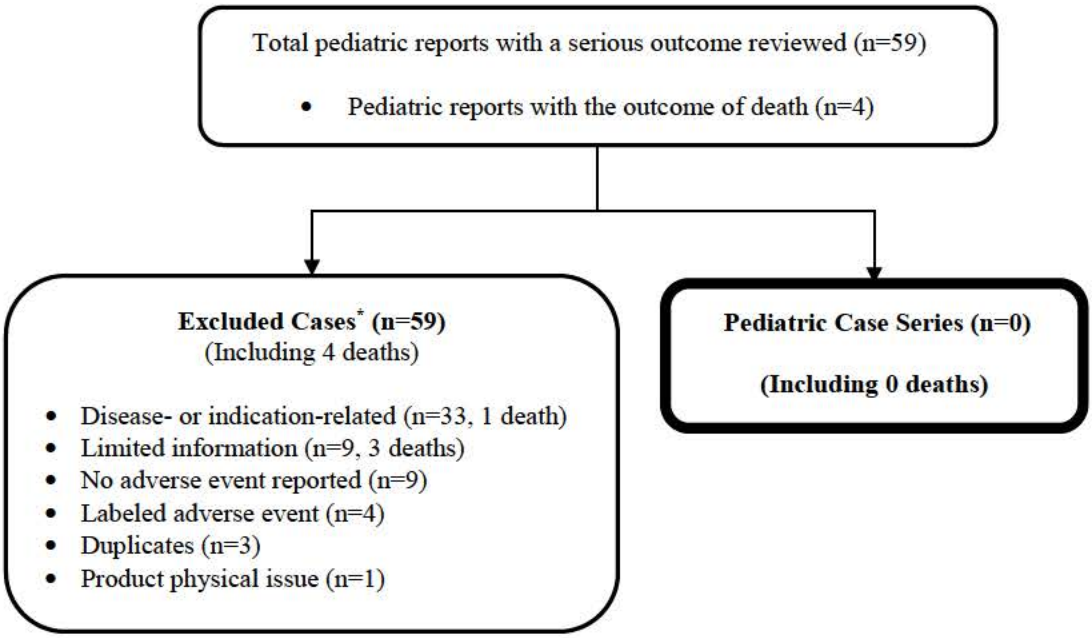
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 59 pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in this section.

Figure 2.2.2 Selection of Serious Pediatric Cases with Pancrelipase Amylase/ Pancrelipase Lipase/ Pancrelipase Protease



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

We retrieved 59 pediatric reports associated with a serious outcome for pancrelipase-containing PEPs in the FAERS database from June 1, 2013 to May 31, 2018. Although the products of interest in this review are Pancreaze and Pertzye, we searched for reports with all pancrelipase-containing PEPs for completeness. The 59 reports contained the following three PEPs: Creon (n=35), Zenpep (n=14), and Pertzye (n=10)[c]; there were no reports with the three other PEPs available in the United States (i.e., Pancreaze, Ultresa, Viokace). All 59 reports were excluded after review; three were duplicates and nine did not contain an adverse event associated with a PEP. See Appendix B for the FAERS case numbers, FAERS version numbers, and manufacturer control numbers for the 59 reports.

The main reason for exclusion was that 33 reports, including one fatal report, contained adverse events that were related to the patient's indication for use of the PEP (EPI) and/or was related to the patient's underlying disease (CF); the patients in these reports had continued symptoms of steatorrhea (n=14) such as abdominal pain, malabsorption, diarrhea, and failure to thrive or

[c] The 10 reports associated with Pertzye use were excluded for the following reasons: disease- or indication-related adverse events (n=6, one report was associated with a fatal outcome), did not contain an adverse event (n=3), and duplicate report (n=1). FAERS case #13028613 was the fatal report.

developed pulmonary infections, pulmonary exacerbations, or unspecified CF exacerbations (n=19). The fatal report described a 14-year-old female with CF who received Pertzye and intermittent Orkambi (lumacaftor/ivacaftor) and passed away from respiratory failure from worsening CF approximately 2 years after Pertzye initiation and 2.5 years after Orkambi initiation.

Nine of 59 reports contained limited information for assessment, including three fatal reports. None of the three fatal reports contained the patient's cause of death. The three reports with a fatal outcome described a 2-year-old female who received Zenpep for an unknown indication and died at an unspecified time relative to Zenpep initiation; a 13-year-old female with CF who passed away sometime while receiving Creon and Dulera (mometasone furoate and formoterol fumarate dihydrate); and a 15-year-old female with CF who was taking Creon and died 8 years prior to the report being received by FDA. The remaining six reports with limited information contained the following adverse events: headache (n=1), pancreatitis (n=1), bowel obstruction (n=1), low blood counts (n=1), liver disorder (n=1), and septic shock and elevated troponin (n=1); the reports did not contain important data elements needed to adequately assess causality such as temporal relationship between the adverse event and PEP initiation, patient comorbidities, concomitant medications, diagnostic evaluation, response to drug dechallenge or rechallenge, and clinical outcome. A representative limited information report of bowel obstruction (FAERS case #12634209) described a 13-year-old male with CF who was receiving Creon, Orkambi (lumacaftor/ivacaftor), and Pulmozyme (dornase alfa) was hospitalized on an unknown date due to a bowel obstruction.

Four reports contained adverse events that are labeled for PEPs, including Pancreaze and Pertzye. Of the four reports, three contained gastrointestinal adverse events (constipation n=1, diarrhea[d] n=1, DIOS n=1) and one report described the event of anaphylaxis to Zenpep in a patient with a gelatin allergy. The single report of DIOS (FAERS case #11894592) was confounded by a concurrent diagnosis of appendicitis and diffuse ileus requiring appendectomy.

Lastly, one case described the product physical issue of "spheres in the capsules are sticking to the inside of the capsule" of Creon (not a product of interest in this review).

3 DISCUSSION

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for pancrelipase-containing PEPs, including the products of interest Pancreaze and Pertzye, in the FAERS database from June 1, 2013 to May 31, 2018. This start date was chosen to capture all reports from the data lock date of a previous review[10] of the pediatric safety of select PEPs, which reviewed adverse event reports through May 31, 2013. We retrieved 59 pediatric

[d] The event of diarrhea was not attributed to the patient's underlying disease because the reporter (nurse) attributed causality to Zenpep and did not report any other information suggesting drug inefficacy; however, it is possible that the event is disease-related.

postmarketing reports, of which 3 were duplicates and 9 did not contain an adverse event associated with a PEP. Of the remaining 47 reports, 33 contained events that were related to the patients underlying EPI or CF, including one fatal report attributed to worsening pulmonary disease. There were nine reports with limited information, including three fatal reports that did not contain the patient's cause of death. There have been major advances in diagnosing and treating CF patients, thereby extending the median survival of patients with CF; an observational analysis of the Cystic Fibrosis Foundation Patient Registry showed that the median survival of children born and diagnosed with CF in 2010 is projected to be 37 years for females and 40 years for males if mortality remains at 2010 levels.[11] However, a subset of patients with CF will still succumb to the illness before age 18.[12] Although unknown, it is possible that the patient's underlying CF was contributory to the three fatal cases with limited information (the death report in a 2-year-old patient did not report the PEP indication for use or patient's medical history, but we presume the indication is CF).

Lastly, four reports contained labeled events for PEPs including gastrointestinal-related adverse events (n=3) and hypersensitivity (n=1). The reports are not unusual in number and no change in severity was noted from review of the reports. FDA required PEPs, which were initially regulated as dietary supplements, to be reviewed and approved NDAs after identifying the safety issue of fibrosing colonopathy. We did not identify any reports of fibrosing colonopathy in this review. We did identify one report of DIOS (n=1), which is labeled in the Adverse Reactions—Postmarketing Experience Section (6.2) of the PEPs labels, but the case of DIOS was confounded by a concurrent diagnosis of appendicitis and ileus.

The products of interest for this review were Pancreaze and Pertzye, although we evaluated all serious reports in pediatric patients with pancrelipase-containing PEPs for completeness. There were no reports in the FAERS database from June 1, 2013 to May 31, 2018 with Pancreaze and 10 reports associated with Pertzye use. Of the 10 reports with Pertzye, three did not contain and adverse event and one was a duplicate. The remaining six reports contained adverse events related to the patient's EPI or CF. No new safety signals were identified with Pancreaze, Pertzye, or any of the remaining four PEPs (Creon, Ultresa, Zenpep, Viokace).

4 CONCLUSION

There is no evidence from these data that there are any pediatric safety concerns with the PEPs of interest in this review, Pancreaze and Pertzye, or any other PEP included in the review (Creon, Ultresa, Zenpep, Viokace).

5 RECOMMENDATIONS

We recommended routine pharmacovigilance monitoring for all pancrelipase-containing PEPs.

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 event 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 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.

6.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=59)

	FAERS Case Number	Version Number	Manufacturer Control Number
1	10284860*	1	BR-ABBVIE-14P-020-1257104-00
2	10309169	1	GB-ABBVIE-14P-167-1260163-00
3	10342393	1	GB-ABBVIE-14P-167-1264153-00
4	10467661	1	US-ABBVIE-14P-163-1285442-00
5	10562776	2	GB-ABBVIE-14P-167-1284270-00
6	10613689	2	GB-ABBVIE-14P-167-1284222-00
7	10614104	2	GB-ABBVIE-14P-167-1284269-00
8	10648550	2	GB-ABBVIE-14P-167-1319929-00
9	10790518	3	US-ABBVIE-15P-163-1342132-00
10	10879975	2	NZ-ABBVIE-15P-118-1354336-00
11	11894592	3	US-WATSON-2015-28664
12	12094584	3	SE-ABBVIE-16P-150-1564408-00
13	12283068	1	US-CTI_01891_2016
14	12334342	1	US-ABBVIE-15P-163-1387159-00
15	12334355	1	US-ABBVIE-15P-163-1409283-00
16	12381566	1	
17	12424416	1	
18	12489495	2	GB-ABBVIE-16P-167-1658532-00
19	12552803	1	
20	12552821	1	
21	12614218	1	
22	12634209	1	
23	12709380	1	
24	12741706	1	
25	12752600*	1	
26	12771023	1	
27	12855898	1	
28	12959049	1	
29	13028613*	4	US-VERTEX PHARMACEUTICALS-2016-006957
30	13038934	1	
31	13129430	1	
32	13357536	1	
33	13384885	1	
34	13514481	1	US-ABBVIE-16P-163-1675939-00
35	13567061	1	
36	13568473	1	
37	13774824	1	
38	13918864	1	
39	13919523	1	
40	13923987	1	

	FAERS Case Number	Version Number	Manufacturer Control Number
41	13930226	3	US-VERTEX PHARMACEUTICALS-2017-004751
42	14019980	1	US-ALLERGAN-1667114US
43	14084308	1	
44	14173372	1	
45	14225316	1	
46	14225380	1	
47	14488313	1	
48	14498993	1	
49	14521351	1	US-VERTEX PHARMACEUTICALS-2018-000968
50	14623661	1	
51	14630448	1	
52	14708266	1	US-ABBVIE-18P-163-2309395-00
53	14742762	1	US-GILEAD-2018-0331811
54	9333364	2	AXC-2013-000238
55	9380393*	1	AXC-2013-000270
56	9416799	1	AXC-2013-000320
57	9436631	1	
58	9437545	1	US-ABBOTT-13P-163-1125804-00
59	9467166	2	AU-ABBOTT-13X-008-1131976-00
* Reports with a fatal outcome.			

7 REFERENCES

[1] Pancreaze (pancrelipase) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; Label revised November 2013.

[2] Pertzye (pancrelipase) [package insert]. Bethlehem, PA: Digestive Care, Inc.; Label revised July 2017.

[3] Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Exp Gastroenterol* 2001;4:55-73.

[4] An effectiveness, safety, and palatability study of pancrelipase microtablets in infants and toddlers with cystic fibrosis and fat malabsorption. (2006). Available at https://clinicaltrials.gov/ct2/show/NCT00217204?term=NCT00217204&rank=1. Accessed on June 11, 2018. (Identification number NCT00217204).

[5] A study of the efficacy and tolerability of pancrelipase microtablet capsules for the treatment of cystic fibrosis-dependent exocrine pancreatic insufficiency. (2009). Available at https://clinicaltrials.gov/ct2/show/NCT00662675?term=NCT00662675&rank=1. Accessed on June 11, 2018. (Identification number NCT00662675).

[6] Med officer review

[7] Evaluation of the safety and efficacy of Pancrecarb® MS-16 in cystic fibrosis. (2007). Available at https://clinicaltrials.gov/ct2/show/NCT00432861?term=NCT00432861&rank=1. Accessed on June 11, 2018. (Identification number NCT00432861).

[8] La T. BCPA pediatric postmarketing adverse event review. September 22, 2001. Accessed on June 12, 2018. Available at https://wayback.archive-it.org/7993/20170114054336/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM288668.pdf

[9] La T, Greene P, Niak A, Hausman ED. Pediatric postmarketing adverse event review. January 4, 2013. Accessed on June 12, 2018. Available at https://wayback.archive-

it.org/7993/20170113232701/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM342183.pdf

[10] La T, Greene P. Pediatric postmarketing adverse event review. October 29, 2013. Accessed on June 12, 2018. Available at https://wayback.archive-it.org/7993/20170113232701/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM342183.pdf

[11] MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the cystic fibrosis foundation patient registry. *Ann Intern Med* 2014;161:233-241.

[12] McColley SA, Schechter MS, Morgan WJ, Pasta DJ, Craib ML, Konstan MW. Risk factors for mortality before age 18 years in cystic fibrosis. *Pediatr Pulmonol* 2017;52:909-915.

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