



Pancreatic Enzymes Therapeutic Class Review (TCR)

January 6, 2022

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January 2022

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Creon® 3,000 ¹	Abbvie	Capsule (EC, DR)	15,000	3,000	9,500	For infants, capsule contents may be administered directly to the mouth or with a small amount of applesauce; prior to each feeding, give 1 capsule (3,000 lipase units) per each 120 mL of formula or before breastfeeding, do not mix capsule contents with breastmilk or formula as this can decrease efficacy
Creon 6,000 ²			30,000	6,000	19,000	Capsule can be opened for patients unable to swallow and sprinkled on soft acidic foods (e.g., applesauce)
Creon 12,000 ³			60,000	12,000	38,000	
Creon 24,000 ⁴			120,000	24,000	76,000	
Creon 36,000 ⁵			180,000	36,000	114,000	
Pancreaze® ⁶	Vivus	Capsule (DR)	15,200	2,600	8,800	Capsule can be opened for patients unable to swallow
			24,600	4,200	14,200	
			61,500	10,500	35,500	For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food such as applesauce; contents should be followed by breast milk or formula but may not be mixed directly into breast milk or formula
			98,400	16,800	56,800	
			83,900	21,000	54,700	
			149,900	37,000	97,300	
Pertzye® 4,000 ⁷	Digestive Care	Capsule (DR)	15,125	4,000	14,375	Only pancreatic enzyme containing bicarbonate-buffered enteric-coated microspheres; capsule can be swallowed whole; for patients unable to swallow capsules can be opened and administered orally or via a gastrostomy tube Pertzye 400 (infants up to 12 months): For infants, capsule contents may be given directly to the mouth or with small amount of acidic food (pH ≤ 4.5; apple-sauce); followed by breast milk or formula but may not be given directly into breast milk or formula
Pertzye 8,000 ⁸			30,250	8,000	28,750	
Pertzye 16,000 ⁹			60,500	16,000	57,500	
Pertzye 24,000 ¹⁰			90,750	24,000	86,250	

FDA-Approved Indications (continued)

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Viokace® 10,440 ¹¹	Allergan/Nestle	Tablet	39,150	10,440	39,150	Tablets should be swallowed whole and not crushed Should not be used in pediatric patients; may result in tablet degradation in the gastric environment which may result in suboptimal growth
Viokace 20,880 ¹²			78,300	20,880	78,300	
Zenpep® 3,000 ¹³	Allergan/Nestle	Capsule (EC, DR)	14,000	3,000	10,000	For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food with a pH ≤ 4.5 such as applesauce
Zenpep 5,000 ¹⁴			24,000	5,000	17,000	Capsule can be opened for patients unable to swallow
Zenpep 10,000 ¹⁵			42,000	10,000	32,000	
Zenpep 15,000 ¹⁶			63,000	15,000	47,000	
Zenpep 20,000 ¹⁷			84,000	20,000	63,000	
Zenpep 25,000 ¹⁸			105,000	25,000	79,000	
Zenpep 40,000 ¹⁹			168,000	40,000	126,000	

DR = delayed release; EC = enteric-coated

Pancreaze, Pertzye, and Zenpep are indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions in both adults and children. Creon is indicated for these conditions, as well as exocrine pancreatic insufficiency due to chronic pancreatitis and pancreatectomy. Other conditions that may result in exocrine pancreatic insufficiency include ductal obstruction from a neoplasm and gastrointestinal bypass surgery. Viokace is indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor in adults only.^{20,21,22,23,24}

OVERVIEW

The exocrine functions of the pancreas include the secretion of pancreatic enzymes necessary for digestion. Pancreatic secretions also neutralize gastric acid in the duodenum and achieve an appropriate pH for maintaining the activity of the enzymes. When this pancreatic function is lost, supplementation of the pancreatic enzymes is needed. Conditions such as cystic fibrosis (CF), chronic pancreatitis, pancreatic tumors, and absence of all or a part of the pancreas are associated with a lack of pancreatic enzymes in the body.

In CF, reduced pancreatic enzyme effects occur due to thickened secretions in the gastrointestinal (GI) tract, specifically the pancreas. Pancreatic enzymes are unable to move into the duodenum, leading to malabsorption of nutrients and malnutrition. This is the main cause of poor growth, fatty diarrhea, and deficiency in fat-soluble vitamins in this population.

Supplemental pancreatic enzymes are available in a variety of formulations and strengths. All formulations are measured by their content of amylase, lipase, and protease. In order to avoid gastric inactivation, enteric coatings and buffering may be used to deliver enzymes to the intestine.

Historically, pancreatic enzyme products were available over-the-counter (OTC). However, due to reports of problems associated with their use, such as intestinal stricture and lack of therapeutic effect, the Food and Drug Administration (FDA) announced that all exocrine pancreatic insufficiency drug products are new drugs and announced the conditions for continued marketing of these drug products.^{25,26} The FDA issued a rule in April 2006 that required manufacturers of pancreatic enzyme drug products to submit new drug applications (NDAs) by April 2009 and receive FDA approval to market their products by April 2010. The FDA subsequently approved Creon and Zenpep in 2009 and Pancreaze in 2010.^{27,28,29} In 2012, the FDA approved the NDAs for Viokace and Pertzeye.^{30,31} In March 2020, the FDA announced withdrawal of the 2006 guidance on exocrine pancreatic insufficiency and corresponding submission of NDAs; the FDA withdrew the guidance because an NDA for these products may not be submitted after March 23, 2020.³² This is because biologics license applications (BLAs) will instead be submitted for proposed pancreatic enzyme products (PEPs). The FDA plans to issue guidance on how information in the withdrawn 2006 guidance would be applicable to proposed PEPs submitted under the Public Health Service Act, including the use of PEPs in BLAs. Until this guidance is available, sponsors interested in submission of a BLA for a PEP are encouraged to contact the Office of New Drugs in FDA's Center for Drug Evaluation and Research with questions. On March 23, 2020, all 5 products included in this therapeutic class review (Creon, Pancreaze, Pertzeye, Viokace, and Zenpep) became former NDAs deemed to be BLAs.³³ Additional details on the "Deemed to be a License" provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), allowing for the transition of these products from NDAs to BLAs, are available in the FDA's corresponding March 2020 final guidance document.³⁴

PHARMACOLOGY³⁵

The enzymes contained in these preparations are amylase, lipase, and protease. They catalyze the hydrolysis of fats to glycerol and fatty acids (lipase), protein into proteoses and protein-derived substances (protease), and starch into dextrans and short-chain sugars (amylase). The natural digestive conditions in the intestine are re-established in this manner. Pancreatic enzymes are a treatment for and not a cure for pancreatic insufficiency.

PHARMACOKINETICS³⁶

Pancreatic enzyme products are not interchangeable due to the differences in their contents and release mechanisms. These enzymes are not absorbed following oral administration but exert their action locally in the GI tract. Pancreatic enzymes are excreted in the feces.

CONTRAINDICATIONS/WARNINGS³⁷

Pancreatic enzymes should not be used in patients who are experiencing acute pancreatitis or acute exacerbation of chronic pancreatitis. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing pancrelipase to patients with gout, renal impairment, or hyperuricemia. Caution is advised when administering pancrelipase to patients with hypersensitivity to proteins of porcine origin since severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with pancreatic enzyme products.

Fibrosing colonopathy is associated with pancreatic enzyme replacement doses > 6,000 lipase units/kg/meal. Per the Cystic Fibrosis Foundation (CFF) Consensus Conferences Guidelines, pancreatic enzyme replacement therapy should not exceed 2,500 lipase units/kg of body weight per meal or greater than 10,000 lipase units/kg of body weight daily in CF patients with pancreatic insufficiency ages 2 through 5 years.^{38,39}

If symptoms of gastrointestinal obstruction occur, investigation into the possibility of bowel stricture, including evaluation of pancreatic enzyme therapy, should be performed. Capsules should not be crushed or chewed. Doing so could dissolve enteric coatings, cause loss of enzymatic activity, and irritate the throat. Capsules can be opened and their contents sprinkled on soft food with a pH of 4.5 or lower. Similarly, tablets should not be held in the mouth or chewed due to the exposure of oral mucosa to enzymes causing irritation to the oral mucosa.

Viokace tablets contain lactose monohydrate and may not be tolerated by patients with lactose intolerance.⁴⁰

With all pancreatic enzymes, there is a theoretical risk for viral transmission.

DRUG INTERACTIONS^{41,42,43,44,45}

No formal drug interaction studies have been conducted nor have interactions been identified.

ADVERSE EFFECTS^{46,47,48,49,50,51}

Common adverse effects to pancreatic enzymes include abdominal pain, nausea, vomiting, flatulence, bloating, cramping, constipation or diarrhea, and cough. Reported skin disorders include pruritus, urticaria, and rash. Hyperuricosuria and hyperuricemia have been associated with higher doses. Colonic strictures have been reported with high-strength preparations (lipase content over 20,000 units per tablet/capsule). Other reported adverse reactions include both hyperglycemia and hypoglycemia, as well as nasopharyngitis. The most serious adverse events reported post-marketing include fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions, including anaphylaxis, asthma, hives, and pruritus.

SPECIAL POPULATIONS^{52,53,54,55,56}

Pediatrics

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase in pediatric patients have been described in the medical literature and through clinical experience.

The safety and effectiveness of Creon have been demonstrated in pediatric patients 12 years and older, and it is commonly used in much younger patients (infants under 12 months of age).

The safety and effectiveness of Zenpep were assessed in pediatric patients aged 1 to 17 years of age.

The safety and effectiveness of Pancreaze were assessed in pediatric patients aged 6 months to 30 months and 8 years to 17 years of age.

The safety and effectiveness of Pertzze were assessed in 10 pediatric patients between 8 and 17 years of age. Dosing is available for patients infants (up to 12 months old), children > 12 months but < 4 years, and children ≥ 4 years and adults.

The safety and effectiveness of Viokace in pediatric patients have not been established. Since Viokace is not enteric-coated, degradation in the gastric environment may result in decreased bioavailability and, therefore, it may be less efficacious than enteric-coated formulations. Consequently, use of Viokace in pediatric patients may increase the risk of inadequate treatment of pancreatic insufficiency and may result in suboptimal weight gain, malnutrition, and/or the need for larger doses of pancreatic replacement enzymes. In addition, the efficacy of Viokace was established in adult patients with concomitant proton pump inhibitor (PPI) therapy.

Dosing of pediatric patients less than 12 years of age should be in accordance with recommended guidance from the Cystic Fibrosis Foundation (CFF) Consensus Guidelines.⁵⁷

Pregnancy

Previously Pregnancy Category C, labeling for all products in this therapeutic class review has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Published case reports of pregnant women using pancrelipase have not shown a drug-associated risk for adverse maternal or fetal outcomes. As these products are minimally absorbed, maternal use is not anticipated to lead to fetal exposure.

DOSAGES^{58,59,60,61,62,63}

Clinical experience should be used in determining the initial starting dose, which should be individualized and adjusted according to fat intake and severity of disease. Fat-ingestion or actual body weight should be taken into consideration when dosing pancreatic enzymes. Prescribing information for different products should be consulted for further guidance. Increasing doses should be done by a healthcare professional and monitored by watching body weight and signs and symptoms of steatorrhea. Pancreatic enzymes should always be taken with food and sufficient fluid. Patients should be adequately hydrated at all times. Pancreatic enzymes are not interchangeable with other pancrelipase products. Guidance from the Cystic Fibrosis Foundation (CFF) Consensus Guidelines may also assist dosing.⁶⁴

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brands in this class and pancreatic enzymes. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

While each agent has demonstrated efficacy to gain FDA-approval, available clinical trials for this class did not meet the criteria for inclusion.^{65,66,67,68,69} The number of patients enrolled was too low to be clinically significant ($n < 55$) and/or the study did not identify the particular products used.

SUMMARY

Pancreatic enzyme supplements differ primarily in enzyme content and bioavailability. In general, these products have demonstrated favorable risk-benefit profiles in the treatment of exocrine pancreatic insufficiency due to cystic fibrosis and other conditions (e.g., chronic pancreatitis). Steps have been taken by the FDA to ensure that these preparations provide safe, effective, and consistent drug delivery. Dosing of these products should be individualized and in accordance with the individual product's prescribing information and the Cystic Fibrosis Foundation (CFF) Consensus Guidelines.

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