Pancreatic Enzymes Review

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Pancreatic Enzymes Review

FDA-Approved Indications[1,2,3,4,5,6,7,8,9]

The products reviewed in this class are indicated for patients with pancreatic exocrine insufficiency, often associated with cystic fibrosis, chronic pancreatitis, ductal obstruction from neoplasm, removal of the pancreas, or gastrointestinal bypass surgery.

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Creon® 6,000	Solvay	Capsule (EC, DR)	30,000	6,000	19,000	Capsule can be opened for patients unable to swallow
Creon® 12,000			60,000	12,000	38,000	
Creon® 24,000			120,000	24,000	76,000	
Pancreaze™	Ortho McNeil Janssen	Capsule (DR)	17,500	4,200	10,000	Capsule can be opened for patients unable to swallow
			43,750	10,500	25,000	
			70,000	16,800	40,000	
			61,000	21,000	37,000	
pancrelipase 5,000 (authorized generic for Zenpep® by Eurand)	X-Gen	Capsule (EC)	27,000	5,000	17,000	Capsule can be opened for patients unable to swallow
Zenpep® 5	Eurand	Capsule (EC)	27,000	5,000	17,000	Capsule can be opened for patients unable to swallow
Zenpep® 10			55,000	10,000	34,000	
Zenpep® 15			82,000	15,000	51,000	
Zenpep® 20			109,000	20,000	68,000	

EC = enteric-coated
DR = delayed release

Overview

The exocrine functions of the pancreas include the secretion of an isotonic fluid that contains, among other things, pancreatic enzymes necessary for digestion. This fluid neutralizes gastric acid in the duodenum and achieves an appropriate pH for maintaining the activity of the enzymes. When this pancreatic function is lost, supplementation of the pancreatic enzymes is needed.

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

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 it announced the conditions for continued marketing of these drug products.[10] The FDA issued a rule 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. On May 7, 2009, the FDA approved the NDA submitted by Solvay Pharmaceuticals, Inc. for Creon.[11] On August 27, 2009, the FDA approved the NDA submitted by Eurand Pharmaceuticals, Inc. for Zenpep.[12] On April 12, 2010, the FDA approved the NDA submitted by Ortho McNeil Janssen for Pancreaze.[13] To date, Creon, Pancreaze and Zenpep are the only three brand-name delayed-release pancreatic enzyme products approved by FDA for U.S. marketing under the process described in the new guidelines.[14] An authorized generic for the 5,000 unit strength of Zenpep is currently distributed by X-Gen Pharmaceuticals.

Pharmacology

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 dextrins and short-chain sugars (amylase). The natural digestive conditions in the intestine are re-established in this manner.

Pharmacokinetics

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/Warnings

Pancreatic enzymes are contraindicated in patients who are hypersensitive to pork products or are experiencing acute pancreatitis or acute exacerbation of chronic pancreatitis.

If symptoms of gastrointestinal obstruction occur, investigation into the possibility of bowel stricture, including evaluation of pancreatic enzyme therapy, should be performed.

Precautions

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 pH greater than 5.5. Similarly, tablets should not be held in the mouth due to the exposure of oral mucosa to enzymes.

Drug Interactions

The serum response to oral iron supplementation may be decreased by concomitant administration of pancreatic enzymes.[15] Calcium carbonate- and magnesium hydroxide–containing antacids may be required to prevent inactivation of pancrelipase (except the enteric-coated dosage forms) in the stomach; however, these antacids may decrease the effectiveness of the pancreatic enzymes.

Adverse Effects

Common adverse effects to pancreatic enzymes include nausea, vomiting, bloating, cramping, and constipation or diarrhea. 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).

Pancreatic enzyme dust or powder is irritating to the nasal mucosa and respiratory tract. It is possible for this dust or powder to precipitate asthma attacks if inhaled.

Special Populations

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 one to 17 years of age.

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

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.

Pregnancy
All products are Pregnancy Category C.

Dosages

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. Prescribing information for different products should be consulted for further guidance. Increasing doses should be monitored by watching body weight and stool fat content. Pancreatic enzymes should always be taken with food. Patients should be adequately hydrated at all times.

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 percent 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/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Available clinical trials for this class did not meet the criteria for inclusion. The number of patients enrolled was too low to be clinically significant (n<50) 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 are being taken by the FDA to ensure that these preparations provide safe, effective and consistent drug delivery.

References

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