



# Pancreatic Enzymes

## Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Creon® 3,000 <sup>1</sup>	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.
Creon® 6,000 <sup>2</sup>			30,000	6,000	19,000	Capsule can be opened for patients unable to swallow.
Creon® 12,000 <sup>3</sup>			60,000	12,000	38,000	
Creon® 24,000 <sup>4</sup>			120,000	24,000	76,000	
Creon® 36,000 <sup>5</sup>			180,000	36,000	114,000	
Pancreaze™ <sup>6</sup>	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) <sup>7</sup>	X-Gen	Capsule (EC)	27,000	5,000	17,000	Capsule can be opened for patients unable to swallow.
Pertzye™ 8,000 <sup>8</sup>	Digestive Care	Capsule (DR)	30,250	8,000	28,750	Capsule can be opened for patients unable to swallow. Only pancreatic enzyme containing bicarbonate-buffered enteric-coated microspheres.
Pertzye™ 16,000 <sup>9</sup>			60,500	16,000	57,500	
Ultresa™ 13,800 <sup>10</sup>	Aptalis	Capsule (DR)	27,600	13,800	27,600	Capsule can be opened for patients unable to swallow.
Ultresa™ 20,700 <sup>11</sup>			41,400	20,700	41,400	
Ultresa™ 23,000 <sup>12</sup>			46,000	23,000	46,000	
Viokace™ 10,440 <sup>13</sup>	Aptalis	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 <sup>14</sup>			78,300	20,880	78,300	

**FDA-Approved Indications (continued)**

Product	Manufacturer	Formulation	Amylase (Units)	Lipase (Units)	Protease (Units)	Notes
Zenpep® 3 <sup>15</sup>	Eurand	Capsule (EC)	16,000	3,000	10,000	For infants, capsule contents may be administered directly to the mouth or with a small amount of acidic food, such as applesauce.
Zenpep® 5 <sup>16</sup>			27,000	5,000	17,000	Capsule can be opened for patients unable to swallow.
Zenpep® 10 <sup>17</sup>			55,000	10,000	34,000	
Zenpep® 15 <sup>18</sup>			82,000	15,000	51,000	
Zenpep® 20 <sup>19</sup>			109,000	20,000	68,000	
Zenpep® 25 <sup>20</sup>			136,000	25,000	85,000	

EC = enteric-coated

DR = delayed release

Pancreaze, Pertzye, Ultresa, 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.<sup>21,22,23,24,25,26</sup>

## 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 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 it announced the conditions for continued marketing of these drug products.<sup>27</sup> 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 for Creon.<sup>28</sup> On August 27, 2009, the FDA approved the NDA submitted by Eurand Pharmaceuticals for Zenpep.<sup>29</sup> On April 12, 2010, the FDA approved the NDA submitted by Ortho McNeil Janssen for Pancreaze.<sup>30</sup> On March 1, 2012 the FDA approved the NDAs submitted by Aptalis Pharma U.S. for Viokace and Ultresa.<sup>31,32</sup> On May 17, 2012 the FDA approved the NDA submitted by Digestive Care for Pertzze.<sup>33</sup> An authorized generic for the 5,000 unit strength of Zenpep is currently distributed by X-Gen Pharmaceuticals.

## PHARMACOLOGY<sup>34</sup>

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.

## PHARMACOKINETICS<sup>35</sup>

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<sup>36</sup>

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 high-dose use of pancreatic enzyme replacement. Per the Cystic Fibrosis Foundation (CFF) Consensus Conferences Guidelines, caution should be exercised when doses of PEPs exceed 2,500 lipase units/kg of body weight per meal or greater than 10,000 lipase units/kg of body weight daily.<sup>37</sup>

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 due to the exposure of oral mucosa to enzymes.

Viokace tablets contain lactose monohydrate and may not be tolerated by patients with lactose intolerance.<sup>38</sup>

## DRUG INTERACTIONS<sup>39,40,41,42,43,44</sup>

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

## ADVERSE EFFECTS<sup>45,46,47,48,49,50</sup>

Common adverse effects to pancreatic enzymes include abdominal pain, nausea, vomiting, flatulence, bloating, cramping, and constipation or diarrhea. 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). 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<sup>51,52,53,54,55,56</sup>

### 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.

The safety and effectiveness of Ultresa were assessed in 40 pediatric patients aged seven years to 17 years of age. Dosing is available for patients 12 months old and greater.

The safety and effectiveness of Pertzye were assessed in ten pediatric patients between eight and 17 years of age. Dosing is available for patients 12 months old and greater.

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 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.<sup>57</sup>

## Pregnancy

All products are Pregnancy Category C.

## DOSAGES<sup>58,59,60,61,62,63,64</sup>

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 pancrealipase products.

## 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 and/or 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 ( $n < 55$ ) 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.

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