

## Therapeutic Class Overview

### Pancreatic Enzymes

#### INTRODUCTION

- Exocrine pancreatic insufficiency occurs in patients with diseases affecting the pancreas including chronic pancreatitis, cystic fibrosis, and carcinomas following resection. As a result of pancreatic enzyme deficiency, patients often develop malnutrition, including low levels of micronutrients, fat-soluble vitamins, and essential fatty acids, as well as weight loss and steatorrhea (*Nakajima et al 2012*).
- In addition to lifestyle modifications, pancreatic enzyme replacement therapy (PERT) with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition (*Nakajima et al 2012*).
- The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol, and free fatty acids, proteins into peptides and amino acids, and starches into dextrans and short chain sugars such as maltose and maltriose.
- Pancrelipase products were available before the 1938 Food, Drug and Cosmetic Act required all new drugs to be subject to new drug applications (NDA). As a result, safety and efficacy studies were never performed with these products. In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and would require the submission and approval of an NDA if manufacturers wished to continue marketing their products. As of April 2010, manufacturers of unapproved pancrelipase products were required to discontinue the manufacturing and distribution of their products, or apply for FDA approval. The most recent version of postmarketing guidance for the use pancreatic enzyme products was updated in October 2016. The FDA does stipulate that these products are not interchangeable (*FDA postmarketing guidance 2016*).
- There are currently 5 available FDA-approved pancrelipase products for the treatment of exocrine pancreatic insufficiency (EPI). The specific FDA-approved indications of the available products are outlined in Table 2.
  - These products primarily differ in their available strengths.
  - All of the pancrelipase products are of porcine origin and contain a mixture of the digestive enzymes lipase, protease, and amylase.
- Due to the potential for enzymatic breakdown in the stomach, most of these products are formulated as enteric-coated, delayed-release capsules to delay drug release until entering the lower digestive tract. One exception is Viokace, which is formulated as a tablet and must be taken in combination with a proton pump inhibitor (PPI).
- The manufacturer dosing recommendations are generally the same across products, as the dosing is in accordance with the Cystic Fibrosis Foundation guidelines. Minor differences may exist for infant dosing based on the smallest strength available for a particular product.
- Consensus clinical guidelines support the use of PERT in the management of chronic pancreatitis and cystic fibrosis (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*). The Cystic Fibrosis Foundation recommends the use of pancreatic enzymes in infants, children, and adults with evidence of pancreatic insufficiency. Pancrelipase is generally dosed based on the lipase units of the formulation and may be calculated as weight-based dosing or on the basis of the fat content of a meal or snack (*Borowitz et al 2009*).
- Medispan Class: Gastrointestinal Agents, Digestive Aids - Digestive Enzymes, Pancrelipase (Lipase-Protease-Amylase)

**Table 1. Medications Included Within Class Review**

Drug	Generic Availability
Creon (pancrelipase)	-
Pancreaze (pancrelipase)	-
Pertzye (pancrelipase)	-
Viokace (pancrelipase)	-
Zenpep (pancrelipase)	-

(*Drugs@FDA 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

Indication	Creon	Pancreaze	Pertzye	Viokase	Zenpep
Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions	✓				
Treatment of EPI due to cystic fibrosis or other conditions		✓	✓		✓
Treatment of adults with EPI due to chronic pancreatitis or pancreatectomy in combination with a PPI				✓	

(Prescribing information: Creon 2020, Pancreaze 2020, Pertzye 2020, Viokase 2020, Zenpep 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Despite relatively recent FDA approval of several pancreatic enzyme products, there are limited clinical studies available (Colombo *et al* 2009, Graff *et al* 2010[a], Graff *et al* 2010[b], Gubergrits *et al* 2011, Toskes *et al* 2011, Trapnell *et al* 2009, Trapnell *et al* 2011, Whitcomb *et al* 2010, Van de Vijver *et al* 2011). To date, only 1 active-comparator study has compared agents head-to-head (Taylor *et al* 2016).
- Colombo *et al* evaluated Creon in patients < 24 months of age with cystic fibrosis and EPI (n = 12). Two weeks treatment with Creon resulted in a significant increase in the mean coefficient of fat absorption (CFA) (the primary endpoint) from 58% at baseline to 84.7% (p = 0.0013). Statistically significant improvements in stool fat content were also reported in the Creon group (p = 0.001) (Colombo *et al* 2009).
- Trapnell *et al* reported a statistically significant improvement in the CFA during a double-blind (DB), short-term, 2-period crossover study of cystic fibrosis patients ≥ 12 years of age (n = 32) with EPI who received Creon treatment compared to patients receiving placebo (88.6% vs 49.6%; p < 0.001) (Trapnell *et al* 2009).
- Creon was studied in 17 pediatric patients 7 to 11 years of age with cystic fibrosis and EPI. In a crossover study design, treatment with Creon was associated with a statistically significant increase in the CFA compared to treatment with placebo (least squares mean [LSM], 82.8% vs 47.4% [standard error {SE}, 2.7% for each]; p < 0.001). Furthermore, Creon was more effective compared to placebo when patients were stratified by their baseline CFA ≤ 50% (p < 0.001) and > 50% (p = 0.008) (Graff *et al* 2010[a]).
- In a 7-day, DB, randomized, placebo-controlled (PC), parallel-group trial of patients ≥ 18 years of age with chronic pancreatitis or total or partial pancreatectomy, those treated with Creon experienced a significantly greater mean ± standard deviation change from baseline in CFA compared to patients treated with placebo (32.1 ± 18.5 vs 8.8 ± 12.5%; p < 0.0001). In addition, statistically significant improvements in coefficient of nitrogen absorption (CNA), stool fat, stool frequency, and stool nitrogen content occurred with Creon treatment (p < 0.005 for all) (Whitcomb *et al* 2010).
- In a 6-month, open-label (OL) extension of the Whitcomb *et al* trial, patients achieved a significantly reduced daily stool frequency compared to baseline (-1 ± 1.3; p < 0.001). Moreover, a greater percentage of patients reported no abdominal pain (66% vs 37.3%), an improvement in abdominal pain (44.7% vs 10.6%) and greater stool consistency compared to baseline (68.1% vs 21.6%; p values not reported) (Gubergrits *et al* 2011).
- Pancreaze was evaluated in a 7-day study of 49 patients with cystic fibrosis and EPI. All patients received Pancreaze during the OL phase and were subsequently randomized to continue on Pancreaze or placebo. Pancreaze treatment significantly improved fat absorption as demonstrated by a significantly lower mean change in CFA between the OL and DB phases for Pancreaze compared to placebo (-1.5% vs -34.1%; p < 0.001) (Trapnell *et al* 2011).
- Pertzye, an enteric-coated, bicarbonate-buffered pancreatic enzyme, was evaluated in a DB, PC, cross-over trial of 24 children and adults with cystic fibrosis and EPI. There was statistically significant improvement in the CFA in active treatment vs placebo (82.5% vs 46.3%, p < 0.001). Stool frequency and stool weight were reduced by 40% and 50%,

respectively, in the active treatment groups as well ( $p < 0.001$  for both). The addition of bicarbonate to the product may increase the release and activation of the enzymes, although no product comparison studies have been done (*Konstan et al 2013*).

- Viokace, the only non-enteric-coated agent in class, was evaluated in a randomized, DB, trial of 50 adults with EPI due to chronic pancreatitis ( $n = 32$ ) or pancreatectomy ( $n = 18$ ). Patients were randomized to pancrelipase (22 tablets/day [20,880 lipase units/tablet]) or placebo, in combination with a PPI, and maintained on a controlled high fat diet of 100 grams of fat/day. After a 72-hour stool collection, the mean CFA was 48% for Viokace -treated patients and 57% for placebo-treated patients after the wash-out period; and at the end of the DB period 86% and 58%, respectively (mean difference, 28%; 95% CI, 21 to 37%;  $p \leq 0.0001$ ) favoring treatment with Viokace (*Micromedex 2020, Viokace prescribing information 2020*).
- *Toskes et al* evaluated 2 doses of Zenpep in 72 patients with chronic pancreatitis and EPI. The mean CFA was significantly higher with low-dose and high-dose Zenpep compared to the placebo run-in period (88.8% vs 89.9% vs 82%;  $p < 0.001$ ); however, there was no statistically significant difference between the 2 doses of Zenpep ( $p = 0.228$ ) (*Toskes et al 2011*).
- One randomized, DB, active-comparator, cross-over, noninferiority trial compared Zenpep and Creon in cystic fibrosis patients aged  $\geq 12$  years living in Europe. Patients had EPI secondary to cystic fibrosis and were stabilized on diet and treatment. A total of 96 patients (89.6% completed study) were randomized to Zenpep or Creon with 25,000 lipase units for 28 days and then each group crossed over to the other treatment with no washout. Zenpep and Creon were considered non-inferior to each other in terms of fat absorption (LSM CFA over 72 hours, 84.1% vs 85.3% [SE, 1.1 for each], respectively;  $p = 0.297$ ). No significant difference in body weight, signs and symptoms of EPI, and patient-reported overall health, perceived well-being, and cystic fibrosis symptoms. The number of patients reporting treatment emergent adverse events were numerically lower for Zenpep (19.6%) vs Creon (25.6%). Overall, the efficacy and safety of Zenpep and Creon were similar (*Taylor et al 2016*).
- A systematic review of 14 trials evaluated the efficacy and safety of PERT in children and adults with CF, compared different formulations of PERT, and their appropriateness in different age groups. Data did not support one PERT formulation was superior to another for outcomes related to weight, height, or body mass index (BMI). In 2 trials ( $n = 41$ ), delayed-release microsphere formulations had less fat in the stool and fewer incidences of abdominal pain. There was no difference between any PERT formulations for any other bowel symptoms (eg, abdominal pain, flatulence, constipation), quality of life, adverse events or for any measure of lung disease. None of the trials reported the number of days in hospital or the incidence of vitamin deficiency (*Somaraju et al 2020*).

## CLINICAL GUIDELINES

- Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the PERT products in accordance with the recommended dosing. Doses of PERT should be commenced at the lowest recommended dose and titrated based on presence of malabsorption to the lowest effective dose (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*).
- The Cystic Fibrosis Foundation guidelines recommend the following growth and weight-status recommendations for children and adolescents (*Stallings et al 2008*):
  - For patients aged  $> 2$  years, energy intakes of 110 to 200% of requirements for healthy patients of similar age, sex, and size results in improved weight gain.
  - Maintenance of a normal weight- and stature-for-age in children, and a normal weight-for-height in adults, was associated with better forced expiratory volume (FEV<sub>1</sub>) and survival.
  - Children and adolescents aged 2 to 20 years should maintain a BMI  $\geq 50$ th percentile. Children aged  $< 2$  years should reach a weight-for-length  $\geq 50$ th percentile by 2 years. For adults, women should maintain a BMI  $\geq 22$  while men should maintain a BMI  $\geq 23$ . These recommendations were based on results showing that maintenance of these growth parameters was associated with higher FEV<sub>1</sub> measurements.
  - For children and adults, PERT dosing should be 500 to 2500 units lipase per kg body weight per meal; or  $< 10,000$  units lipase per kg body weight per day; or  $< 4000$  units lipase per gram dietary fat.

## SAFETY SUMMARY

- Pancreatic enzyme products have no known contraindications.
- The warnings and precautions associated with pancrelipase products include allergic reactions, fibrosing colonopathy, hyperuricemia, oral mucosal irritation, and viral exposure.
- There is a theoretical risk of viral transmission with all pancreatic enzyme products.
- The most common adverse effects with pancrelipase are diarrhea, dyspepsia, neck pain, and nasal congestion. Serious adverse effects associated with pancrelipase include fibrosing colonopathy, hyperuricemia, and lymphadenopathy.
- No significant drug interactions have been identified with pancrelipase.
- Viokace tablets contain lactose monohydrate and may not be tolerated by patients who have lactose intolerance.
- Irritation of the oral mucosa may occur if pancreatic enzyme products are retained in the mouth. After administration, the mouth should be inspected and rinsed with water, milk, or formula if necessary to remove product remaining on the oral mucosa ([Katkin et al 2020](#)).
- A pediatric postmarketing pharmacovigilance review of the 5 pediatric enzyme products was conducted by the FDA for any adverse events with serious outcomes during the period of June 2013 to May 2018. There was no evidence from these data to suggest that there any pediatric safety concerns with the pediatric pancreatic enzymes; routine monitoring is recommended with these agents (*FDA postmarketing pharmacovigilance review 2018*).

## DOSING AND ADMINISTRATION

- The FDA has updated questions and answers for healthcare professions regarding the approved use of pancreatic enzyme products. In terms of switching a patient from 1 pancreatic enzyme product to another, the guidance suggests considering initiating therapy with a similar amount of lipase, and then adjusting based on patient response. Adjustments to a new dose may take 1 to 2 weeks depending upon the patient. Individual responses should be monitored (*FDA postmarketing guidance 2016*).

**Table 3. Dosing and Administration**

Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
Creon (pancrelipase)	Delayed-release capsule: 3000/9500/15,000 units 6000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units	<p><u>Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (adults and children ≥ 4 years old):</u> Initial: 500 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children &gt; 12 months and &lt; 4 years old):</u> Initial: 1000 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (infants ≤ 12 months old):</u> 3000 lipase units (1 capsule) per 120 mL of formula or breast-feeding</p>	<p>For infants &lt; 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration</p> <p>Take with meals and snacks with sufficient fluid.</p> <p>Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food, such as applesauce.</p>

Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
Pancreaze <sup>†</sup> (pancrelipase)	Delayed-release capsule: 2600/6200/10,850 units 4200/14,200/24,600 units 10,500/35,500/61,500 units 16,800/56,800/98,400 units 21,000/54,700/83,900 units	<p>Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old):</u> Initial: 500 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (children &gt; 12 months and &lt; 4 years old):</u> Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (infants ≤ 12 months old):</u> 2600 lipase units (1 capsule) per 120 mL of formula or per breast-feeding</p> <p>Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.</p>	<p>For infants &lt; 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration</p> <p>Take with meals and snacks with sufficient fluid.</p> <p>Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food with a pH of 4.5 or less, such as applesauce.</p>
Pertzye (pancrelipase)	Delayed-release capsule: 4000/14,375/15,125 units 8000/28,750/30,250 units 16,000/57,500/60,500 units 24,000/86,250/90,750 units	<p><u>Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old and weight ≥ 16 kg):</u> Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (children &gt; 12 months but &lt; 4 years old and weight ≥ 8 kg):</u> Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (infants up to 12 months):</u> 4000 lipase units (1 capsule) per 120 mL of formula or per breast feeding</p>	<p>For infants &lt; 12 months old, capsule contents may be administered directly to the mouth prior to each feeding; do not mix capsule contents directly into formula or breast milk prior to administration.</p> <p>Take with meals and snacks with sufficient fluid.</p> <p>Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food with a pH of 4.5</p>



Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
		<p>Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.</p>	<p>or less, such as applesauce.</p> <p>Consume the entire capsule contents immediately. Careful not to crush the microsphere contents.</p>
<p>Viokace (pancrelipase)</p>	<p>Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units</p>	<p><u>Treatment of adults with EPI due to chronic pancreatitis or pancreatectomy in combination with a PPI:</u> Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p>Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.</p>	<p>Take with meals and snacks with sufficient fluid.</p> <p>Swallow tablet whole.</p> <p>Tablets are not enteric coated and should be taken in combination with a PPI.</p>
<p>Zenpep (pancrelipase)</p>	<p>Delayed-release capsule: 3000/10,000/14,000 units 5000/17,000/24,000 units 10,000/32,000/42,000 units 15,000/47,000/63,000 units 20,000/63,000/84,000 units 25,000/79,000/105,000 units 40,000/126,000/168,000 units</p>	<p><u>Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old):</u> Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (children &gt; 12 months but &lt; 4 years old):</u> Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or &lt; 4000 lipase units/g fat ingested per day</p> <p><u>Treatment of EPI due to cystic fibrosis or other conditions (infants ≤ 12 months old):</u> 3000 lipase units (1 capsule) per 120 mL of formula or breast-feeding</p> <p>Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.</p>	<p>For infants &lt; 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration</p> <p>Take with meals and snacks with sufficient fluid.</p> <p>Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food, with a pH of 4.5 or less such as applesauce.</p>

See the current prescribing information for full details

\*Dosage expressed as lipase/protease/amylase

†Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences. Pancreaze should be administered per recommendations with 1 exception. The Conferences recommend doses of 2000 to 4000 lipase units in infants up to 12 months. Pancreaze is available in a 2600 lipase unit capsule. The recommended dose of Pancreaze is contained correctly within the table.

## CONCLUSION

- There are currently 5 available pancrelipase products indicated as PERTs for the treatment of EPI due to cystic fibrosis, chronic pancreatitis, and other conditions. These agents include Creon, Pancreaze, Pertzze, Viokace, and Zenpep. Of these, Creon and Viokace are also approved for EPI resulting from pancreatectomy. Creon, Pancreaze, Pertzze, and Zenpep are approved for use in infants less than 12 months of age. The safety and efficacy of Viokace in children have not been established.
- All of these products with the exception of Viokace are formulated as enteric-coated, delayed-release capsules to prevent their breakdown in the stomach and enhance drug release in the duodenum. Viokace is formulated as a tablet and must be taken in combination with a PPI. Viokace may not be tolerated in patients with lactose intolerance.
- The approval of these products resulted from the FDA's decision to require all manufacturers of pancrelipase products to submit a NDA and receive approval for continued marketing and manufacturing. Historically, the generic pancrelipase products were available before the Food, Drug and Cosmetic Act required the safety and efficacy of a drug to be established before marketing.
- Limited available clinical studies have demonstrated that pancrelipase is associated with statistically significant improvements in the CFA, CNA, and stool frequency and consistency compared to placebo. Studies were generally of short duration, enrolled only a small number of patients, and have not demonstrated clinically meaningful differences between treatments (*Colombo et al 2009, Graff et al 2010[a], Graff et al 2010[b], Gubergrits et al 2011, Taylor et al 2016, Toskes et al 2011, Trapnell et al 2009, Trapnell et al 2011, Whitcomb et al 2010, Van de Vijver et al 2011*).
- Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the PERT products in accordance with each product's recommended dosing (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*).

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