Therapeutic Class Overview
Pancreatic Enzymes

Therapeutic Class

- **Overview/Summary:** Pancreatic exocrine insufficiency occurs in patients with diseases affecting the pancreas including chronic pancreatitis, cystic fibrosis and carcinomas following resection. Patients with pancreatic enzyme deficiency often develop malnutrition, weight loss and steatorrhea. Pancreatic enzyme replacement therapy with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition.[1] The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose.[2-7] The safety and efficacy of generic pancrelipase products were never formally established, as they were available prior to the 1938 Food, Drug and Cosmetic Act which required all new drugs be the subject of a new drug application (NDA).[8] In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and will require the submission and approval of an NDA if manufacturers wished to continue marketing their products. As of April 2010, manufacturers of unapproved pancreatic enzyme products were required to discontinue the manufacturing and distribution of their products, or apply for FDA-approval.[8]

  There are currently six pancrelipase products FDA-approved for the treatment of exocrine pancreatic insufficiency including Creon®, Pancreaze®, Pertyze®, Ultresa®, Viokace® and Zenpep®.[2-7] These products primarily differ in their available strengths. Viokace® is only indicated for adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy, and its safety and efficacy in children has not been established.[6] 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, these products are formulated as enteric-coated capsules to delay drug release until entering the lower digestive tract.[2-7] Viokace® is the only agent that is not enteric-coated; however, it must be administered with a proton pump inhibitor to reduce gastric pH and prevent enzymatic break down. The manufacturer dosing recommendations are the same across all 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. The respective strengths of each product, classified by units of lipase/protease/amylase, are listed in Table 1.

Table 1. Current Medications Available in the Therapeutic Class[2-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Pancrelipase (Creon®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions	Delayed-release capsule: 3,000/9,500/15,000 units 6,000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units	-
Pancrelipase (Pancreaze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 4,200/10,000/17,500 units 10,500/25,000/43,750 units 16,800/40,000/70,000 units 21,000/37,000/61,000 units	-
Pancrelipase (Pertyze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 8,000/28,750/30,250 units 16,000/57,500/60,500 units	-
Pancrelipase (Ultresa®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or	Delayed-release capsule: 13,800/27,600/27,600 units	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	other conditions	20,700/41,400/41,400 units 23,000/46,000/46,000 units	
Pancrelipase (Viokace®)	Treatment of adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor	Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units	-
Pancrelipase (Zenpep®*)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 3,000/10,000/16,000 units 5,000/17,000/27,000 units 10,000/34,000/55,000 units 15,000/51,000/82,000 units 20,000/68,000/109,000 units 25,000/85,000/136,000 units	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Despite recent Food and Drug Administration-approval of several pancreatic enzyme products, there are limited clinical studies available.
- Clinical studies evaluating the safety and efficacy of Creon® have consistently demonstrated an increase in the coefficient of fat absorption, coefficient of nitrogen absorption, stool frequency and consistency when compared to placebo. Furthermore, Creon® has been studies in patients with cystic fibrosis, chronic pancreatitis and with patients who have undergone pancreatectomy.[9-15]
- Pancreaze® was evaluated in a seven-day study of patients with cystic fibrosis and exocrine pancreatic insufficiency. All patients received Pancreaze® during the open-label phase and were subsequently randomized to continue on Pancreaze® or placebo. Pancreaze® treatment significantly improved fat absorption as demonstrated by a significant reduction in fat absorption for patients randomized to placebo following withdrawal of Pancreaze® during the randomization period (P<0.001).[16]
- Toskes et al evaluated two doses of Zenpep® in 72 patients with chronic pancreatitis and exocrine pancreatic insufficiency. The mean coefficient of fat absorption was significantly higher with both doses of Zenpep® compared to the placebo run-in period (P<0.001); however, there was no statistically significant differences between the two doses (P=0.228).[17]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Pancreatic enzyme supplementation is indicated in patients with chronic pancreatitis and exocrine pancreatic insufficiency.[18]
  - Clinical improvement in nutritional parameters and the normalization of gastrointestinal symptoms are sufficient criteria to evaluate the efficacy of pancreatic enzymes.[18]
  - Pancreatic enzyme replacement therapy should be administered to all infants, children and adults with cystic fibrosis and evidence of pancreatic exocrine insufficiency.[19-21]
  - In general, patients will need 500 to 4,000 lipase units per gram of fat ingested per day. Dosing enzymes according to how much fat is eaten per meal is more likely to mimic the body's own response of adjusting pancreatic enzyme excretion relative to how much fat is present in a meal. Alternatively, dosing may be calculated based on patient bodyweight.[19-21]
  - Doses above 6,000 lipase units/kg/meal have been associated with colonic strictures in children less than twelve years of age, whether standard strength enzymes or high-strength pancreatic enzymes were taken.[19-21]
- Other Key Facts:
  - An authorized generic product is available for the 5,000 unit dose of Zenpep®.[22]

- The approved pancreatic enzyme replacement therapies are not bioequivalent and are not interchangeable with one another.[22]
- The pancrelipase products primarily differ with respect to their concentrations of lipase, lipase and amylase in each dosage formulation.

References

1. Nakajima K, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. Core Evid. 2012;7:77-91.
2. Creon® [package insert]. North Chicago (IL): AbbVie Inc.; 2013 Mar.
3. Pancreaze® [package insert]. Titusville (NJ): Janssen Pharmaceuticals Inc.; 2011 Sep.
4. Zenpep® [package insert]. Bridgewater (NJ): Aptalis Pharma US Inc.; 2013 Apr.
5. Ultresa® [package insert]. Birmingham (AL): Aptalis Pharma US Inc.; 2012 Mar.
6. Viokace® [package insert]. Birmingham (AL): Aptalis Pharma US Inc.; 2012 Mar.
7. Pertyze® [package insert]. Bethlehem (PA): Digestive Care Inc.; 2012 May.
8. Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products–Submitting NDAs [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2006 Apr [cited 2012 Sep 10]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf.
9. Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas. 2009 Aug;38(6):693-9.
10. Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis: an open-label, multicentre, single-treatment-arm study. Clin Drug Investig. 2010;30(6):351-64.
11. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2009 Dec;8(6):370-7.
12. Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged seven to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther. 2010 Jan;32(1):89-103.
13. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010 Oct;105(10):2276-86.
14. Toskes PP, Secci A, Thieroff-Ekerdt R; ZENPEP Study Group. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011 Apr;40(3):376-82.
15. Gubergrits N, Malecka-Panas E, Lehman GA, Vasileva G, Shen Y, Sander-Struckmeier S, et al. A six-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Aliment Pharmacol Ther. 2011 May;33(10):1152-61.
16. Trapnell BC, Strausbaugh SD, Woo MS, Tong SY, Silber SA, Mulberg AE, et al. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2011 Sep;10(5):350-6.
17. Toskes PP, Secci A, Thieroff-Ekerdt R; ZENPEP Study Group. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011 Apr;40(3):376-82.
18. Frulloni L, Falconi M, Gabbrielli A, Gaia E, Graziani R, Pezzilli R, et al. Italian consensus guidelines for chronic pancreatitis. Dig Liver Dis. 2010 Nov;42 Suppl 6:S381-406.
19. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009 Dec;155(6 Suppl):S73-93.
20. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H; Clinical Practice Guidelines on Growth and Nutrition Subcommittee. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008 May;108(5):832-9.
21. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr. 1995 Nov;127(5):681-4.
22. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2012 [cited 2012 Sep 10]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Therapeutic Class Review
Pancreatic Enzymes

Overview/Summary

Pancreatic exocrine 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, essential fatty acids as well as weight loss and steatorrhea.[1] In addition to lifestyle modifications, pancreatic enzyme replacement therapy with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition.[1] The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose.[2-7] Pancrelipase products were available since before the 1938 Food, Drug and Cosmetic Act began requiring all new drugs be the subject of a new drug application (NDA). As a result, safety and efficacy studies were never performed with these products.[8] In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and will 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.[8]

There are currently six pancrelipase products FDA-approved for the treatment of exocrine pancreatic insufficiency including Creon®, Pancreaze®, Pertyze®, Ultresa®, Viokace® and Zenpep®.[2-7] These products primarily differ in their available strengths. Viokace® is only indicated for adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy, and its safety and efficacy in children has not been established.[6] 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, these products are formulated as enteric-coated, delayed-release capsules to delay drug release until entering the lower digestive tract.[2-7] Viokace® is the only agent that is not enteric-coated; however, it must be administered with a proton pump inhibitor to reduce gastric pH and prevent enzymatic break down. An authorized generic product is available for the 5,000 unit dose of Zenpep®.[9] The manufacturer dosing recommendations are the same across all 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 pancreatic enzyme replacement therapy in the management of chronic pancreatitis and cystic fibrosis.[10-13] 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 the fat content of a meal or snack.

Medications

Table 1. Medications Included Within Class Review[2-7]

Generic Name (Trade name)	Medication Class	Generic Availability
Pancrelipase (Creon®)	Digestive enzyme	-
Pancrelipase (Pancreaze®)	Digestive enzyme	-
Pancrelipase (Pertyze®)	Digestive enzyme	-
Pancrelipase (Ultresa®)	Digestive enzyme	-
Pancrelipase (Viokace®)	Digestive enzyme	-
Pancrelipase (Zenpep®*)	Digestive enzyme	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[2-7]

Generic Name	Treatment of Exocrine Pancreatic Insufficiency Due to Cystic Fibrosis, Chronic Pancreatitis, Pancreatectomy or Other Conditions	Treatment of Exocrine Pancreatic Insufficiency Due to Cystic Fibrosis or Other Conditions	Treatment of Adults with Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis or Pancreatectomy in Combination with a Proton Pump Inhibitor
Pancrelipase (Creon®)	✔		
Pancrelipase (Pancreaze®)		✔	
Pancrelipase (Pertyze®)		✔	
Pancrelipase (Ultresa®)		✔	
Pancrelipase (Viokace®)			✔
Pancrelipase (Zenpep®*)		✔	

Pharmacokinetics

Table 3. Pharmacokinetics[2-7,14]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Pancrelipase (Creon®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Pancreaze®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Pertyze®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Ultresa®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Viokace®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Zenpep®)	Negligible	Not reported	Not reported	Not reported	Not reported

Clinical Trials

The clinical studies evaluating the safety and efficacy of the pancreatic enzyme products for their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[15-23] Despite recent FDA-approval of several pancreatic enzyme products, there are limited clinical studies available.

Colombo et al evaluated Creon® in patients <24 months of age with cystic fibrosis and exocrine pancreatic insufficiency (N=12). Following two weeks of treatment with Creon®, the mean coefficient of fat absorption, the primary endpoint, was significantly higher in patients receiving Creon® therapy compared to patients receiving placebo (84.7 vs 58.0%; *P*=0.0013). Statistically significant improvements in stool fat content were also reported in the Creon® group (*P*=0.001).[15] Trapnell et al reported a statistically significant improvement in coefficient of fat absorption during a short-term study of cystic fibrosis patients ≥12 years of age with exocrine pancreatic insufficiency who received Creon® treatment compared to

[patients receiving placebo (88.6 vs 49.6%; *P*<0.001).[17] Creon® was studied in 17 pediatric patients seven to 11 years of age with cystic fibrosis and exocrine pancreatic insufficiency. In a crossover study design, treatment with Creon® was associated with a statistically significant increase in coefficient of fat absorption compared to treatment with placebo (82.8 vs 47.4%; *P*<0.001). Furthermore, Creon® was more effective compared to placebo when patients were stratified by their baseline coefficient of fat absorption ≤50% (*P*<0.001) and >50% (*P*=0.008).[18] In a seven-day study of patients ≥18 years of age with chronic pancreatitis or total or partial pancreatectomy, those treated with Creon® experienced a significantly greater change from baseline in coefficient of fat absorption 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, stool fat, stool frequency and stool nitrogen content occurred with Creon® treatment (*P*<0.005 for all).[19] In a six-month extension study, these patients were able to achieve a significantly reduced stool frequency compared to baseline (*P*<0.001). Moreover, a greater percentage of patients reported no abdominal pain (66.0 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).[20]

Pancreaze® was evaluated in a seven-day study of patients with cystic fibrosis and exocrine pancreatic insufficiency. All patients received Pancreaze® during the open-label phase and were subsequently randomized to continue on Pancreaze® or placebo. Pancreaze® treatment significantly improved fat absorption as demonstrated by a significant reduction in fat absorption for patients randomized to placebo following withdrawal of Pancreaze® during the randomization period (*P*<0.001).[21]

Toskes et al evaluated two doses of Zenpep® in 72 patients with chronic pancreatitis and exocrine pancreatic insufficiency. The mean coefficient of fat absorption was significantly higher with both doses of Zenpep® compared to the placebo run-in period (*P*<0.001); however, there was no statistically significant differences between the two doses (*P*=0.228).[22]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Colombo et al[15] Pancrelipase (Creon®) dose not reported	OL Infants and children <24 months of age with CF and exocrine pancreatic insufficiency and CFA >70%	N=12 8 weeks	Primary: CFA after two weeks of treatment Secondary: Not reported	Primary: After two weeks of treatment with pancrelipase, there was a statistically significant increase in the mean CFA from baseline (84.7 vs 58.0%; *P*=0.0013). There was a statistically significant reduction in mean stool fat (from 13.3 to 5.3 g/d; *P*=0.001) and mean fecal energy loss (from 238.5 to 137.9 kJ/d; *P*=0.018) after two weeks of pancrelipase treatment. Dietary fat intake did not change, whereas an improvement was observed in stool frequency and characteristics. Patient weight and height increased over eight weeks of treatment with pancrelipase No serious adverse event was reported. Secondary: Not reported
Graff et al[16] Pancrelipase (Creon®) 8,000 lipase units/kg daily in divided doses All patients continued their baseline pancreatic enzyme replacement therapy treatment for three days to establish baseline values.	MC, OL, Infants and children <7 years of age (>3.75 kg) with CF and exocrine pancreatic insufficiency who were currently taking a pancreatic enzyme product at baseline	N=19 Up to 14 days	Primary: Safety compared to standard therapy Secondary: Ease of drug dosing and efficacy compared to standard therapy	Primary: Nine patients (50%) experienced at least one treatment-related adverse event with each treatment. No patients discontinued the study due to a treatment related adverse event. One adverse event judged possibly related to treatment by the investigator was diaper rash, which occurred in one patient taking the study drug. The treatment-emergent adverse events in both groups were considered by the investigators to be mild in severity. No serious adverse events were reported and no deaths occurred. Clinical symptom assessment (abdominal pain, stool consistency and flatulence) and mean daily stool frequency during each assessment period on study drug and standard therapy suggested similar efficacy between treatments. There was slightly more day-to-day variability (significance not tested) in mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				daily stool frequency when patients were receiving standard therapy compared to study drug. No changes in vital, bodyweight or body mass index were reported between the treatments. Secondary: Overall, 33.3% of caregivers reported that the study drug was easier to accurately dose compared to the standard therapy, 61.6% of caregivers rated the study drug the same as standard therapy and 6.5% of caregivers believed dosing was harder with the study drug compared to standard therapy. The stool fat percentage was similar among patients treated with the study drug compared to their standard therapy at baseline (28.1 vs 27.9%, respectively; *P* value not reported). Total fat intake and total calorie intake remained similar during the study drug and standard therapy assessment periods (*P* value not reported).
Trapnell et al (abstract)[17] Pancrelipase (Creon®) 4,000 lipase units/g fat vs placebo	DB, PC, RCT, XO Patients ≥12 years of age with CF and exocrine pancreatic insufficiency	N=not reported 10 days	Primary: CFA Secondary: CNA, symptoms and safety	Primary: Pancrelipase was associated with a significantly higher mean CFA compared to placebo (88.6 vs 49.6%; *P*<0.001). Secondary: The mean CNA was significantly greater with pancrelipase compared to placebo (85.1 vs 49.9%; *P*<0.001). Symptoms were improved and fewer treatment-emergent adverse events were reported with pancrelipase compared to placebo. One patient discontinued for weight loss unrelated to study drug.
Graff et al[18] Pancrelipase (Creon®) 4,000 lipase units/g fat (using 12,000 unit capsules)	DB, MC, PC, RCT, XO Patients aged 7 to 11 years of age with CF and exocrine	N=17 10 days	Primary: Change in CFA Secondary: Change in CNA, assessment of clinical symptoms,	Primary: The least squares mean CFA values following treatment was significantly higher for patients treated with pancrelipase compared to patients treated with placebo (82.8 vs 47.4%; *P*<0.001). In patients with a CFA ≤50% at baseline, significant increases in CFA occurred with pancrelipase compared to placebo (81.8 vs 37.3%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo To maintain normal nutrition, each patient received an individualized, prospectively designed diet containing ≥40% of calories derived from fat.	pancreatic insufficiency who were receiving therapy with a commercially available pancreatic enzyme product at a stable dose for >3 months, in a clinically stable condition, without evidence of acute respiratory disease, for ≥1 month before enrollment, stable body weight (decline ≤5% within three months of enrollment)		CGI and tolerability	Similarly, in patients with a baseline CFA >50%, there was a significant increase in CFA for patients treated with pancrelipase compared to placebo (84.5 vs 64.3%; *P*=0.008). Secondary: Overall, treatment with pancrelipase significantly increased CNA compared to placebo (80.3 vs 45.0%; *P*<0.001). In patients with a CFA ≤50% at baseline, there was a significant increase in CNA with pancrelipase treatment compared to placebo (79.8 vs 34.6%; *P*<0.001). Similarly, in patients with a baseline CFA >50%, there was a significant increase in CFA for patients treated with pancrelipase compared to placebo (81.2 vs 62.3%; *P*=0.008). Compared to the placebo group, patients randomized to receive pancrelipase experienced statistically significant improvements in stool fat (g), stool weight (g), stool nitrogen (g) and daily stool frequency (*P*<0.001 for all). Treatment-emergent adverse events were reported in five patients (29.4%) taking pancrelipase and nine patients taking placebo (56.3%). Gastrointestinal events were more prevalent during placebo-treatment compared to pancrelipase treatment. No patients discontinued treatment due to a treatment-emergent adverse event and no serious events were reported. No clinically relevant treatment differences in laboratory parameters or vital signs were noted.
Whitcomb et al[19] Pancrelipase (Creon®) 12,000 lipase unit capsules administered as six capsules per meal and three capsules per	DB, MC, PC, PG, RCT Patient ≥18 years of age with confirmed chronic pancreatitis or	N=54 7 days	Primary: Change from baseline in CFA Secondary: Change from baseline in CNA,	Primary: There was a significantly greater change from baseline in CFA for patients treated with pancrelipase compared to patients receiving placebo (32.1±18.5 vs 8.8±12.5%; *P*<0.0001). Secondary: The change from baseline in CNA was significantly greater in the pancrelipase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
snack vs placebo Prior to randomization, all patients entered a five-day placebo run-in period to establish baseline.	total or partial pancreatectomy >180 days prior to enrolment and confirmed exocrine pancreatic insufficiency, determined by abnormal secretin tests, faecal elastase <100 1g/g, 72-hour faecal fat determination (>15 g/day) or total pancreatectomy		stool fat, stool nitrogen, clinical symptomatology and safety	group compared to the placebo group (97.7±82.3 vs 24.4±101.0%; *P*=0.0013). The least squares mean change from baseline in stool frequency per day in the pancrelipase group was significantly lower than patients treated with placebo (-0.6±0.2 vs 0.2±0.2; *P*=0.005). Pancrelipase was associated with statistically significant reductions in stool fat content compared to placebo (-147.6±12.7 vs -34.8±11.5 g; *P*<0.0001). The stool nitrogen content was significantly lower following treatment with pancrelipase compared to treatment with placebo -54.5±7.9 vs -8.0±7.1 g; *P*<0.0001). Treatment-related adverse events were reported in five (20.0%) patients receiving pancrelipase and six (20.7%) patients treated with placebo. Adverse events were mostly gastrointestinal in nature. One patient in each group had adverse events thought by the investigator to be related to treatment, including abnormal feces, frequent bowel movements and inadequate diabetes control. No patients discontinued treatment due to an adverse event. No deaths or changes in laboratory parameters were reported.
Gubergrits et al[20] Pancrelipase (Creon®) 24,000 lipase unit capsules administered in individualized doses as determined by study investigator	ES, MC, OL Patient ≥18 years of age with confirmed chronic pancreatitis or total or partial pancreatectomy >180 days prior to enrolment and confirmed exocrine pancreatic insufficiency,	N=51 6 months	Primary: Clinical symptomatology, CGI of disease, quality of life and safety Secondary: Not reported	Primary: The mean stool frequency was 2.8±1.3 at baseline and 1.8±0.9 at six months, resulting in an overall mean change of -1.0±1.3 (*P*<0.001). Overall, the proportion of patients reporting no abdominal pain increased from 37.3% at baseline to 66.0% after six months. An improvement in abdominal pain was more common compared to complaints of worsening (44.7 vs 10.6%). For stool consistency, the percentage of subjects with formed/normal stools increased from 21.6% at baseline to 68.1% at six months. Improvement in stool consistency was recorded in 55.3%; only 4.3% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	determined by abnormal secretin tests, faecal elastase <100 1g/g, 72-hour faecal fat determination (>15 g/day) or total pancreatectomy			recorded worsening of stool consistency. The percentage of subjects with no flatulence increased from 15.7% at baseline to 44.7% at the end of the study. Improvements in flatulence were observed 48.9% of patients whereas 12.8% of patients reported worsening of flatulence. Results of a subgroup analysis demonstrate no clinically meaningful difference between patients with chronic pancreatitis or pancreatic surgery with regard to stool frequency, abdominal pain, stool consistency and flatulence. The proportion of patients with no symptoms or mild symptoms overall increased from 49.1% at baseline to 83.0% at six months. No clinically meaningful changes from baseline to study end were detected in any of the eight domains or summary scores of the quality of life survey. Treatment-emergent adverse events were reported 43.1% of patients. The most common classification of adverse events was gastrointestinal disorders (17.6%) and infections and infestations in 13.7%. The most common treatment-emergent adverse events overall were anemia, abdominal pain, pyrexia, bronchitis and sinusitis. No clinically significant changes from baseline in laboratory and nutritional parameters were observed. Secondary: Not reported
Trapnell et al (abstract)[21] Pancrelipase (Pancreaze®) does not reported vs placebo	PC, RCT Patients with CF and exocrine pancreatic insufficiency	N=49 7 days	Primary: Change in CFA between OL and RCT phases Secondary: Not reported	Primary: Patients receiving pancrelipase improved fat absorption as demonstrated by a significantly lower mean change in CFA between OL and DB phases compared to patients receiving placebo (1.50±5.88 vs -34.10±23.03%; *P*<0.001). Protein absorption was also improved in patients receiving pancrelipase. No unexpected adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients entered an OL, ≤14 day run-in phase, maintained a high-fat diet (100 ± 15 g/day), and received Pancreaze® (10,500 or 21,000 units). Participants with a CFA ≥80% were then entered into the randomized phase for seven days.				Secondary: Not reported
Toskes et al (abstract)[22] Pancrelipase (Zenpep®) 20,000 lipase units administered seven times daily (high-dose) vs pancrelipase (Zenpep®) 5,000 lipase units administered seven times daily (low-dose) All patients completed a two-day placebo run-in period to establish baseline CFA.	DB, DR, RCT, XO Patients with chronic pancreatitis and exocrine pancreatic insufficiency	N=72 11 days	Primary: CFA between OL and RCT phases, CNA, body weight and days with exocrine pancreatic insufficiency symptoms Secondary: Not reported	Primary: Mean CFA was significantly higher with low- (88.9%) and high-dose (89.9%) pancrelipase compared to the placebo run-in period (82%; *P*<0.001). There was no statistically significant difference in CFA between the two pancrelipase doses (*P*=0.228). In patients with baseline CFA <90% (n=33), the high dose was associated with a significantly higher CFA compared to the low dose (84.1 vs 81.1%; *P*<0.001). Significant improvements in CNA (*P*<0.001), body weight (*P*≤0.021), and body mass index (*P*≤0.020) occurred with both doses compared to baseline values. The percentage of days with exocrine pancreatic insufficiency symptoms decreased with both doses. Secondary: Not reported
Van de Vijver et al[23] 500 lipase units/kg/meal vs	PG, RCT, SB Infants 6 to 30 months of age with CF with a	N=18 11 days	Primary: Weight change, change from baseline in CFA, percentage of	Primary: The median change in weight at the end of the study was 0.05 kg (range, -0.1 to 0.2) in the 500 unit group, 0.30 kg (range, -0.1 to 0.7) in the 1,000 unit group, -0.05 kg (range, -0.2 to 0.1) in the 1500 unit group and 0.15 kg (range, -0.3 to 0.5) in the 2,000 unit group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,000 lipase units/kg/ meal vs 1,500 lipase units/kg/ meal vs 2,000 lipase units/kg/ meal	history of abnormal CFA or lower than 15 µg fecal elastase per gram of stool, confirming a diagnosis of CF-related pancreatic insufficiency		carbon dioxide expired and safety Secondary: Not reported	The change from baseline in mean CFA were -2% in the 500 unit group, 1% in the 1,000 unit group, -1% in the 1,500 unit group and -2% in the 2,000 unit group. During the run-in period the median cumulative carbon dioxide expiration, a marker of lipase activity, was 11 (range, -8 to 59). After randomization, the median cumulative percentage of carbon dioxide expired was 18 (range, 14 to 23) in the 500 unit, 14 (range, -1 to 17) in the 1,000 unit, 10 (range, 10 to 27) in the 1,500 unit and 3 (range, 1 to 49) in the 2,000 unit groups, respectively. There were two reports of abdominal pain, one of abnormal stools and one complaint of increased bowel movement in the 500 unit/kg/meal group. One patient randomized to the 1,000 unit/kg/meal group experienced constipation. In the 2,000 unit/kg/meal group, vomiting and rhinitis were reported in one patient each. Secondary: Not reported

Study abbreviations: DB=double-blind, DR=dose-response, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: CF=cystic fibrosis, CFA=coefficient of fat absorption, CGI=clinical global impression, CNA=coefficient of nitrogen absorption

Special Populations

Table 5. Special Populations[2-7,14]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pancrelipase (Creon®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Pancreaze®)	Safety and efficacy in elderly patients have not been established. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Pertyze®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Ultresa®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Viokace®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pancrelipase (Zenpep®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.

Adverse Drug Events

Table 6. Adverse Drug Events[2-7,14]

Adverse Event	Pancrelipase					
	Creon®	Pancreaze®	Pertyze®	Ultresa®	Viokace®	Zenpep®
Central Nervous System						
Dizziness	4	-	-	-	-	-
Early satiety	-	-	-	-	-	6
Headache	-	-	-	7	3	✔
Dermatologic						
Allergic reaction	✔	✔	✔	✔	✔	✔
Anal pruritus	-	-	-	-	7	-
Pruritus	✔	✔	✔	✔	✔	✔
Rash	✔	✔	✔	✔	3	✔
Urticaria	✔	✔	✔	✔	✔	✔
Gastrointestinal						
Abnormal feces	4	-	-	-	-	-
Abdominal pain	4	10	✔	✔	3	18
Constipation	✔	✔	✔	✔	✔	✔
Diarrhea	-	✔	10	-	-	-
Distal intestinal obstruction syndrome	✔	✔	✔	✔	✔	✔
Dyspepsia	-	-	10	-	-	-
Fibrosing colonopathy	✔	✔	✔	✔	✔	✔
Flatulence	4	5	✔	✔	3	6
Frequent bowel movements	4	-	-	-	-	-
Nausea	✔	✔	✔	✔	✔	✔
Vomiting	6	✔	-	-	-	-
Upper abdominal pain	-	5	-	-	-	-
Musculoskeletal						
Ear pain	-	-	-	11	-	-
Muscle spasm	✔	-	-	-	-	-
Myalgia	✔	-	-	-	-	-
Neck pain	-	-	-	14	-	-
Pharyngolaryngeal pain	-	-	-	7	-	-
Other						
Anemia	-	-	-	-	3	-
Ascites	-	-	-	-	3	-

Adverse Event	Pancrelipase					
	Creon®	Pancreaze®	Pertyze®	Ultresa®	Viokace®	Zenpep®
Asymptomatic transaminase elevations	✔	-	-	-	-	-
β-hemolytic streptococcal infection	-	-	-	11	-	-
Biliary tract stones	-	-	-	-	7	-
Blurred vision	✔	-	-	-	-	-
Contusion	-	-	-	-	-	6
Cough	4	-	10	-	-	6
Epistaxis	-	-	-	7	-	-
Hydrocholecystis	-	-	-	-	3	-
Hyperglycemia	8	-	-	-	-	-
Hyperuricemia	✔	✔	✔	✔	✔	✔
Hypoglycemia	4	-	-	-	-	-
Lymphadenopathy	-	-	-	11	-	-
Nasal congestion	-	-	-	14	-	-
Nasopharyngitis	4	-	-	-	-	-
Peripheral edema	-	-	-	-	-	3
Recurrence of pre-existing carcinoma	✔	✔	✔	✔	✔	✔
Renal cyst	-	-	-	-	3	-
Viral infection	-	-	-	-	3	-
Weight decrease	-	-	-	-	-	6

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications
There are no contraindications to the pancreatic enzyme products.

Warnings/Precautions

Table 7. Warnings and Precautions[2-7,14]

Warning/Precaution	Pancrelipase (Creon®, Pancreaze®, Pertyze®, Ultresa®, Viokace®, Zenpep®)
Allergic reactions; exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin	✔
Fibrosing colonopathy; use caution when doses exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)	✔
Hyperuricemia; use caution, as porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels	✔
Oral mucosal irritation; do not chew or retain in the mouth	✔
Viral exposure; pancrelipase is sourced from pancreatic tissue and there is a theoretical risk for transmission of viral disease	✔

Drug Interactions
There are no well-documented drug interactions with the pancreatic enzyme products.

Dosage and Administration

All strengths and formulations below are listed as units of lipase/protease/amylase.

Table 8. Dosing and Administration[2-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Pancrelipase (Creon®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day; individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (infants <12 months old): Delayed-release capsule: 3,000 lipase units (one capsule) per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children >12 months and <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children ≥4 years old: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 3,000/9,500/15,000 units 6,000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units
Pancrelipase (Pancreaze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other	Delayed-release capsule: 4,200/10,000/17,500 units 10,500/25,000/43,750 units

Generic Name	Adult Dose	Pediatric Dose	Availability
	other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	conditions (infants <12 months old): Delayed-release capsule: 2,000 to 4,000 lipase units per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months and <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	16,800/40,000/70,000 units 21,000/37,000/61,000 units
Pancrelipase (Pertyze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old and weight ≥8 kg): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other	Delayed-release capsule: 8,000/28,750/30,250 units 16,000/57,500/60,500 units

Generic Name	Adult Dose	Pediatric Dose	Availability
		conditions (children ≥4 years old and weight ≥16 kg): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	
Pancrelipase (Ultresa®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old and weight ≥14 kg): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old and weight ≥28 kg): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 13,800/27,600/27,600 units 20,700/41,400/41,400 units 23,000/46,000/46,000 units
Pancrelipase (Viokace®)	Treatment of adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor: Tablet: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat	Safety and efficacy in children patients have not been established.	Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units

Generic Name	Adult Dose	Pediatric Dose	Availability
	ingested per day		
Pancrelipase (Zenpep®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (infants <12 months old): Delayed-release capsule: 3,000 lipase units per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 3,000/10,000/16,000 units 5,000/17,000/27,000 units 10,000/34,000/55,000 units 15,000/51,000/82,000 units 20,000/68,000/109,000 units 25,000/85,000/136,000 units

Clinical Guidelines

As of April 2010, all marketed pancreatic enzyme replacement therapies must have been approved by the Food and Drug Administration. As a result, unapproved generic products were removed from the market. Some of the clinical guidelines highlighted below recommend the use of generic pancreatic enzyme replacement therapies; however, these guidelines were published prior to the removal of the generic products from the marketplace.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Italian Association for the Study of the Pancreas: **Italian Consensus Guidelines for Chronic Pancreatitis (2010)**[10]	Treatment of chronic pancreatitis • Pancreatic enzyme supplementation is indicated in patients with chronic pancreatitis and exocrine pancreatic insufficiency. • Quantitative measurement of fecal fat is not mandatory for prescribing pancreatic enzymes. • Pancreatic enzyme supplementation improves the quality of life in chronic pancreatitis. • Pancreatic enzyme supplementation is not recommended for reducing frequency and severity of painful relapses in chronic pancreatitis. • Proton pump inhibitors should be added if steatorrhea is not controlled by pancreatic enzyme supplementation alone. • Pancreatic enzyme formulations with enteric-coated pH-sensitive minimicrosphere and high lipase content should be used. • The recommended dose is 25,000 to 40,000 units of lipase per meal. Pancreatic enzymes should be administered during or just after meals. • The clinical improvement of the nutritional parameters and the normalization of gastrointestinal symptoms are sufficient criteria to evaluate the efficacy of pancreatic enzymes. • Assessment of endocrine pancreatic function is recommended by measuring fasting blood glucose levels. • Pancreatic enzyme supplementation is recommended in surgically treated patients with pancreatic exocrine insufficiency.
The Cystic Fibrosis Foundation: **Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009)**[11]	Pancreatic function and pancreatic enzymes • For infants with cystic fibrosis under two years of age, pancreatic functional status should be measured by fecal elastase or coefficient of fat absorption in all individuals. • For infants with cystic fibrosis under two years of age, pancreatic enzyme replacement therapy should be started in the following patients: o All infants with two cystic fibrosis transmembrane conductance regulator mutations associated with pancreatic insufficiency. o All infants with fecal elastase <200 mg/g or coefficient of fat absorption <85% (in infants <6 months of age), or other objective evidence of pancreatic insufficiency. o In infants with unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. • In infants with cystic fibrosis under two years of age, pancreatic enzyme therapy should not be initiated in infants with one or two cystic fibrosis transmembrane conductance regulator mutations associated with pancreatic sufficiency unless: o An objective test of pancreatic function indicates fat malabsorption. o The infant has unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. • Pancreatic enzyme replacement therapy should be initiated at a dose of 2,000 to 5,000 lipase units at each feeding, adjusted up to a dose of no greater than 2,500 lipase units per kg per feeding with a maximum daily dose of 10,000 lipase units per kg.

Clinical Guideline	Recommendations
	• Generic, non-proprietary pancreatic enzyme replacement therapy should not be used.
The Cystic Fibrosis Foundation: **Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review (2008)**[12]	• Dosing should be as follows: 500 to 2,500 units of lipase per kilogram body weight per meal; or <10,000 units of lipase per kilogram body weight per day; or <4,000 units of lipase per gram dietary fat per day. • For children and adults, there is insufficient evidence regarding the efficacy of generic pancreatic enzyme preparations and, therefore, the use of proprietary pancreatic enzyme preparations for pancreatic enzyme replacement therapy is recommended. • The absence of evidence-based recommendations highlights the need for well-designed studies of both branded and generic preparations and dosing and important clinical outcome variables.
The Cystic Fibrosis Foundation: **Use of Pancreatic Enzyme Supplements for Patients with Cystic Fibrosis in the Context of Fibrosing Colonopathy (1995)**[13]	• Patients with pancreatic insufficiency should consume a high-calorie diet with unrestricted fat, which is appropriate for age and clinical status. Additional calories will be required for catch-up growth. • A nutritional assessment should be performed regularly as a component of routine care of patients with cystic fibrosis, and additionally, when dosing of pancreatic enzyme replacement is altered. • Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. This provides approximately 450 to 900 lipase units per gram of fat ingested. • Dosing enzymes per gram of fat ingested provides consistent guidelines for all ages. • In general, patients will need 500 to 4,000 lipase units per gram of fat ingested per day. Dosing enzymes according to how much fat is eaten per meal is more likely to mimic the body's own response of adjusting pancreatic enzyme excretion relative to how much fat is present in a meal. • An alternative dosing regimen based on body weight may be used although it is less physiologic. This method is a practical way to determine the number of enzyme capsules needed per meal. This avoids shifting dosing schedules, which may be confusing for some caretakers, or may be difficult for some patients to understand. Weight-based enzyme dosing should begin with 1,000 lipase units/kg/meal for children less than four years of age, and at 500 lipase units/kg/meal for those over four years of age. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two to three snacks per day. • Doses above 6,000 lipase units/kg/meal have been associated with colonic strictures in children less than twelve years of age, whether standard strength enzymes or high-strength pancreatic enzymes were taken. Patients currently on higher doses (>2,500 lipase units/kg/meal or 4,000 lipase units/gram fat ingested/day) should be evaluated and either immediately decreased, or titrated down to a lower dosage range. • The enteric-coating prevents inactivation of enzymes in the acidic gastric environment. The dissolution profile of generic microcapsules may not be equivalent to proprietary brands despite identical enzyme content. • A poor response to therapy can be defined as continued abdominal

Clinical Guideline	Recommendations
	complaints (such as bloating; flatus; abdominal pain; loose, frequent stools or overt diarrhea) along with symptomatic steatorrhea (bulky, oily, foul stools) and/or poor growth despite treatment with pancreatic enzymes. Abdominal pain alone does not indicate the need for an increase in enzyme dosage. Before increasing the enzyme dose above the recommended range, one should consider factors which may cause these symptoms, but which will not respond to increasing the enzyme dose.

Conclusions

The Food and Drug Administration (FDA) has approved six pancrelipase products indicated as pancreatic enzyme replacement therapies for the treatment of pancreatic exocrine insufficiency due to cystic fibrosis, chronic pancreatitis and other conditions. These agents include Creon®, Pancreaze®, Pertyze®, Ultresa®, Viokace® and Zenpep®. Of these, Creon® is also approved for pancreatic exocrine insufficiency resulting from pancreatectomy. Creon®, Pancreaze® and Zenpep® are approved for use in infants less than 12 months of age, while Pertyze® and Ultresa® may be used in children >12 months of age.[2-7] The safety and efficacy of Viokace® in children has not been established.[6] 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.[2-7] The recent approval of these products results from the FDA's decision to require all manufacturers of pancrelipase products to submit a new drug application and receive approval for continued marketing and manufacturing of pancrelipase products. 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.[8]

Limited available clinical studies have demonstrated that pancrelipase is associated with statistically significant improvements in the coefficient of fat absorption, coefficient of nitrogen absorption and stool frequency and consistency compared to placebo.[15-23] These studies were generally of short duration and enrolled only a small number of patients. No head to head studied have been conducted comparing the FDA-approved pancrelipase products. Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the pancreatic enzyme replacement products in accordance with the recommended dosing.[10-13] An authorized generic product is available for the Zenpep® 5,000 unit capsule.[9]

References

1. Nakajima K, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. Core Evid. 2012;7:77-91.
2. Creon® [package insert]. North Chicago (IL): AbbVie Inc.; 2013 Mar.
3. Pancreaze® [package insert]. Titusville (NJ): Janssen Pharmaceuticals Inc.; 2011 Sep.
4. Zenpep® [package insert]. Bridgewater (NJ): Aptalis Pharma US Inc.; 2013 Apr.
5. Ultresa® [package insert]. Birmingham (AL): Aptalis Pharma US Inc.; 2012 Mar.
6. Viokace® [package insert]. Birmingham (AL): Aptalis Pharma US Inc.; 2012 Mar.
7. Pertyze® [package insert]. Bethlehem (PA): Digestive Care Inc.; 2012 May.
8. Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products–Submitting NDAs [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2006 Apr [cited 2012 Sep 10]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf.
9. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2012 [cited 2012 Sep 10]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
10. Frulloni L, Falconi M, Gabbrielli A, Gaia E, Graziani R, Pezzilli R, et al. Italian consensus guidelines for chronic pancreatitis. Dig Liver Dis. 2010 Nov;42 Suppl 6:S381-406.
11. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009 Dec;155(6 Suppl):S73-93.
12. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H; Clinical Practice Guidelines on Growth and Nutrition Subcommittee. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008 May;108(5):832-9.
13. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr. 1995 Nov;127(5):681-4.
14. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2012 Sep 10]. Available from: http://www.thomsonhc.com/.
15. Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas. 2009 Aug;38(6):693-9.
16. Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis: an open-label, multicentre, single-treatment-arm study. Clin Drug Investig. 2010;30(6):351-64.
17. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2009 Dec;8(6):370-7.
18. Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged seven to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther. 2010 Jan;32(1):89-103.
19. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010 Oct;105(10):2276-86.
20. Gubergrits N, Malecka-Panas E, Lehman GA, Vasileva G, Shen Y, Sander-Struckmeier S, et al. A six-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Aliment Pharmacol Ther. 2011 May;33(10):1152-61.

21. Trapnell BC, Strausbaugh SD, Woo MS, Tong SY, Silber SA, Mulberg AE, et al. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2011 Sep;10(5):350-6.
22. Toskes PP, Secci A, Thieroff-Ekerdt R; ZENPEP Study Group. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011 Apr;40(3):376-82.
23. Van de Vijver E, Desager K, Mulberg AE, Staelens S, Verkade HJ, Bodewes FA, et al. Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. J Pediatr Gastroenterol Nutr. 2011 Jul;53(1):61-4.