Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Pancreatic Enzyme Replacement Products (PEP)

Month/Year of Review: November 2012

Last Review: September 2010
Source: Provider Synergies

Current Status of PDL Class:
- Preferred Agents: CREON®, ZENPEP®, LIPASE/PROTEASE/AMYLASE
- Non Preferred Agents: VIOKASE®, ULTRESA®, PANCRELIPASE®, PERTZYE®, PANCREAZE®

Research Questions:
- Is pancrelipase effective in the treatment of exocrine pancreatic insufficiency?
- Is pancrelipase safe in the treatment of exocrine pancreatic insufficiency?
- Is there evidence that one pancrelipase product is more effective or safer than another product?

Conclusions:
- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzymes in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change ir CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).[4,5]
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which ca potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Othe side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.

Recommendations:
- Due to no apparent difference in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration issues.
- Evaluate comparative costs in executive session.

Reason for Review: Since the last review, three forms of pancrealipase have gained approval through the FDA mandated new drug application process (Ultresa®, Pertyze®, and Viokase®). This review will evaluate the efficacy and safety of pancreatic enzyme replacement products (PEPs).

Previous HRC Conclusions:

- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- Recommend inclusion of at least one agent in this class in accordance with FDA recommendations.

Background/Summary:

A number of chronic conditions can contribute to the ongoing loss of pancreatic tissue, which in turn, interrupts the normal production of exocrine pancreatic enzymes (EPI). EPI is often associated with steatorrhea, bloating, nausea, pain, diabetes mellitus, abnormal gastric motility, decreased absorption of nutrients, and decreased weight.[1] Implications of reduced nutrient absorption include retarded growth and development, impaired immune response, infections, and bleeding tendencies. The most common causes of EPI are cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic trauma. Patients with these conditions often rely on administration of exogenous pancreatic enzyme replacement therapy (PEP).[14]

The porcine pancrelipase products which make up PEPs, contain lipase, protease, and amylase which catalyze the hydrolysis of fats to monoglycerol, glycerol, and fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars, respectively.[14] The site of pharmacologic action is at the duodenum and small intestine, and there is little systemic absorption. This is a life-long therapy for patients who require pancreatic enzyme replacement and these patients may be at risk for fibrosing colonopathy, which is associated with high dose lipase exposure.[14]

Treatment with PEPs has traditionally been an effective method of managing EPI. [1] PEPs were available as over-the-counter products prior to the Federal Food, Drug, and Cosmetic Act of 1938 and the Drug Efficacy Study Implementation amendment in 1962. Thus, PEP manufacturers were not required to prove safety or efficacy of products that were currently on the market. Among the marketed products, there were substantial variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands. The FDA later deemed that PEPs should be available by prescription only since such product variability could adversely affect the safety and effectiveness of the PEPs, and use of these products required continuous physician monitoring of patients.[14]

In 2004, the FDA announced that all PEPs are to be considered new drugs, and that manufacturers who wish to continue to market PEPs must submit New Drug Applications (NDAs). [1,14] In 2006, the Agency released additional guidance to for PEP manufacturers, defining requirements for drug development in this class. A PEP drug development program could rely on a single adequate and well-controlled study to demonstrate safety and efficacy, but patient populations should include at a minimum, an efficacy study in pediatric patients with CF. Meaningful endpoints could be pharmacodynamic measures such as decrease in steatorrhea as evaluated in a 72-hour quantitative stool collection. Study design could be a randomized, two-period, placebo-controlled, crossover study in as few as 10-25 patients with CF, and the duration of the entire trial could be days to 2 to 3 weeks. The primary efficacy endpoint used in most studies included the coefficient of fat absorption (CFA), however two different methods of measuring CFA were used. Creon was the first marketed PEP in the US to be approved under an NDA.[14]

Author: Brandy Fouts, Pharm.D.

Table 1: Available products[7-13]

Drug Products (Manufacturer)	FDA approval and Manufacturer [a]	FDA approved indications	Amylase (Units)	Lipase (Units)	Protease (Units)	Dosage Form	Other Considerations
Creon 3,000	2009 Solvay	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.	15,000	3,000	9,500	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Creon 6,000			30,000	6,000	19,000		
Creon 12,000			60,000	12,000	38,000		
Creon 24,000			120,000	24,000	76,000		
Zenpep 3	2009 Eurand	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis and other conditions	16,000	3,000	10,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Zenpep 5			27,000	5,000	17,000		
Zenpep 10			55,000	10,000	34,000		
Zenpep 15			82,000	15,000	51,000		
Zenpep 20			109,000	20,000	68,000		
Zenpep 25			136,000	25,000	85,000		
Viokace	2012 Aptalis Pharma	Exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy	39,150	10,440	39,150	Tablet	Tablets must be swallowed whole. Do not crush or chew.
Viokace			78,300	20,880	78,300		
Ultresa	2012 Aptalis Pharma	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	27,600	13,800	27,600	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Ultresa			41,400	20,700	41,400		
Ultresa			46,000	23,000	46,000		
Pancrelipase	2009 X-Gen Pharmaceuticals	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions	27,000	5,000	17,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pancrelipase			55,000	10,000	34,000		
Pancrelipase			82,000	15,000	51,000		
Pancrelipase			109,000	20,000	68,000		
Pertzye	2012 Digestive Care	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	30,250	8,000	28,750	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pertzye			60,500	16,000	57,500		
Pancreaze	2010 Janssen Pharmaceuticals	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	17,500	4,200	10,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pancreaze			43,750	10,500	25,000		
Pancreaze			70,000	16,800	40,000		
Pancreaze			61,000	21,000	37,000		

Author: Brandy Fouts, Pharm.D.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCT's) comparing PEP's to placebo or other products was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. A total of 24 RCTs and 3 systematic reviews resulted from initial search. After further review, five RCT's were included in review. Main reasons for exclusion were non-meaningful study outcomes, inadequate blinding, redundancy in trials, and irrelevant reason for use (feeding tube clogs).

Efficacy Analysis: (Evidence table in Appendix A)
A randomized, multicenter, double-blind, placebo-controlled, poor quality, parallel group trial (n=27) evaluated the effects on steatorrhea of Creon 10 versus placebo in 27 patients with CP. The primary objective of the study was to compare Creon 10 to placebo in the control of steatorrhea after a 2 week washout phase, which was measured using the mean change in CFA from baseline. Secondary objectives were the evaluation of stool parameters and global improvement of symptoms scales. Patients in the Creon 10 group had a higher mean change in CFA compared to placebo (36.7% vs. 12.1% respectively, p=0.0185). Patients in the Creon 10 group had improved stool consistency (p=0.0102) and decreased stool frequency (p=0.0015). The daily fat excretion decreased significantly more in the Creon 10 patients versus placebo (-56.6 g/d vs. -11.4 g/d, p=0.0181). Global disease symptom scores were evaluated by both physicians and patients. Physicians perceived a greater global disease symptom scores in the Creon 10 group versus placebo (p=0.0425) but this was not statistically significant for subject scores (p=0.0634). This study was discontinued early due to slow recruitment.[2]

A double-blind, randomized, placebo-controlled, two-arm, parallel-group trial (n=54) evaluated the efficacy of delayed-release pancrelipase capsules in patients ≥ 18 years old with EPI due to CP or pancreatic surgery (PS). A single-blind placebo run-in period preceded randomization; baseline measurements were recorded at this time. After the placebo run-in, patients were discharged to home for up to 16 days where they could use any pancreatic enzyme replacement regimen. Eligible patients were then randomized to double-blind treatment with either pancrelipase or placebo for 7 days, taken orally with meals. Dieticians worked with study subjects to ensure consumption of ≥80 g of fat each day. The primary outcome was the change in CFA from baseline to the end of the double-blind treatment period. Two patients did not complete the trial and were excluded from analysis. The mean change from baseline in CFA was 32.1% ± 18.5 for patients treated with pancrelipase, compared to 8.8%±12.5 for patients in the placebo group (p<0.0001). Patients in the pancrelipase group also experienced a greater change in CNA from baseline [97.7±82.3 for the pancrelipase group vs. 24.4±101 for the placebo group (p=0.0013)]. There were few treatment emergent adverse events (TEAEs) recorded for both groups. Five (20%) patients in the pancrelipase group and 6 (20.7%) patients in the placebo group reported at least one TEAE, consisting mainly of GI events (abnormal feces, flatulence, abdominal pain/discomfort). There were no discontinuations due to adverse events or deaths reported during this study.[3]

A double, blind, randomized, placebo-controlled, two-period crossover study (n=32) of Creon 24 versus placebo was conducted in patients with CF and EPI. The primary outcome was the CFA and secondary outcomes were coefficient of nitrogen absorption (CNA), symptoms, and safety. Prior to study initiation, patients

were given an individualized diet by a dietitian that contained at least 100 g/day of fat and included 40% of total calories from fat. Subjects were then randomized 1:1 to one of two crossover treatment sequences: Creon then placebo or placebo then Creon. The Creon 24 capsules were dosed to achieve 4,000 lipase units/g fat. The CFA [least squares (LS) mean] was 88.6% in the Creon group compared to 49.6% in the placebo group ($p<0.001$). Similar results were observed for LS mean of the CNA, with 85.1% in the Creon group compared to 49.9% in the placebo group ($p<0.001$). The LS mean for stool fat, stool nitrogen, and stool weight were all found to favor the Creon group versus placebo ($p<0.001$ for all). There were fewer adverse effects in the Creon group. Adverse effects seen in both the Creon and placebo groups were flatulence, abdominal pain, weight loss, and headache. The only adverse effects seen in Creon subjects and not the placebo group were dizziness and cough.[4]

A double-blind, placebo-controlled study evaluated the efficacy and tolerability of pancrelipase delayed-release 12,000-lipase unit capsules in patients aged 7 to 11 years old with EPI due to CF. This study was a 2-period cross-over trial that was designed to evaluate the difference in the mean change from baseline in CFA compared to placebo (n=17). Each patient received an individualized, prospectively designed diet containing ≥40% of calories derived from fat. Patients eligible for the study received pancreatic enzyme replacement therapy (PERT) for 2 weeks, and then were randomized to treatment or placebo for another two weeks and a baseline measurement was taken. Patients received placebo or treatment for 5 days before crossing-over to the alternative treatment. After a washout period of 14 days, in which patients received their usual PERT, patients entered a second crossover period in which procedures were identical to the first cross-over period. The primary efficacy outcome, overall CFA, was measured on the 2nd and 5th day of each cross-over period. Results show that patients who were treated with this formulation of pancrelipase had significantly increased CFA compared to those treated with placebo [treatment difference=35.4% ($p<0.001$)]. Absorption of nitrogen, measured as a secondary endpoint, was also statistically greater in patients receiving pancrelipase compared to placebo [treatment difference = 35.3% ($p<0.001$)]. TEAEs were reported in 5 patients (29.4%) during pancrelipase treatment and in 9 patients (56.3%) during receipt of placebo. Gastrointestinal adverse events were more prevalent during the receipt of placebo [4 patients (25%)] and there were no TEAEs considered to be related to pancrelipase treatment. No serious TEAEs or discontinuations were reported in this study.[5]

A double-blind, randomized, placebo-controlled, withdrawal study investigated the efficacy and safety of Pancreaze in CF patients aged 7 to 60 with established EPI. The study started with a 7-day screening phase, followed by $\leq$ 14-day open-label run-in phase, and was followed by a 4-7 day placebo-controlled, double-blind, withdrawal phase. During the screening phase and after laboratory assessments, patients stopped taking their current pancreatic enzyme regimen, and started on a high fat diet (100 ± 15g fat/day or 3 g/kg/day), and Pancreaze was administered based on lipase requirement during the previous 3 days. Forty-eight participants were initially enrolled. Only patients with a CFA>80% (n=40) continued the study and were randomized to continue Pancreaze (n=20) or switch to placebo (n=20). The primary efficacy endpoint was change in percent CFA between 72-hour stool collections at the end of open-label phase and double-blind phase, which favored the Pancreaze group (-1.5%± 5.9) compared to placebo (-34.1%± 23; $p<0.001$). Results were similar between adults and pediatric patients. Similar results were found for protein absorption. TEAs were similar between placebo and Pancreaze. The most common adverse events were abdominal pain and bloating.[6]

Safety/tolerability:

In general, common adverse effects to pancreatic enzymes include nausea, vomiting, bloating, cramping and constipation or diarrhea. Hyperuricosuria and hyperuricemia have been associated with higher doses. Caution should be used in patients with gout, hyperuricemia, or renal impairment.[7-13] Case reports of

colonic strictures have been reported with high-strength preparations (lipase content over 20,000 units per tablet/capsule). Caution is recommended when doses exceed 2500 units/kg/meal or 10,000 units/kg/day.[1]

Creon- The most common adverse effects were hyperglycemia (8%), hypoglycemia (4%), abdominal pain (4%), abnormal feces (4%), flatulence (4%), frequent bowl movements (4%), and nasopharyngitis (4%) which were slightly more common than placebo.[7]

Zenpep- The most common adverse effects were abdominal pain (18%), flatulence (6%), headache (15%), contusion (6%), weight decreased (6%), cough (6%), and early satiety (6%), which were slightly more common than placebo.[8]

Viokace- The most common adverse effects were anemia (3%), anal pruritus (7%), abdominal pain (3%), ascites (3%), flatulence (3%), edema peripheral (3%), biliary tract stones (7%), hydrocholecystis (3%), viral infection (3%), headache (3%), renal cyst (3%), and rash (3%), which did not occur in the placebo group.[9]

Ultresa- The most common adverse effects were headache (7%), pharyngolaryngeal pain (7%), and epistaxis (7%) which were slightly more common than placebo.[10]

Pancrelipase – The most common adverse effects were abdominal pain (18%), flatulence (6%), headache (15%), contusion (6%), decreased weight (6%), which were all less common than placebo.[11]

Pertzye- The most common adverse effects were diarrhea (10%), dyspepsia (10%), and cough (10%), which were slightly more common than placebo.[12]

Pancreaze – The most common adverse effects were abdominal pain (10%) and flatulence (5%), which were all less common than placebo.[13]

High quality Systematic Reviews:

No meta-analyses or high quality systemic reviews have been performed on pancreatic enzyme products.

Pharmacology:[7-13]
Pancreatic enzyme products contain amylase, lipase, and protease, which act as replacements for digestive enzymes secreted by the pancreas. These enzymes are beneficial in patients with inadequate pancreatic secretions (e.g. cystic fibrosis) who require assistance in the digestion of proteins, starches, and fats in the duodenum and proximal small intestines.

Pharmacokinetics:[7-13]
Pancreatic enzyme products are not interchangeable due to the differences in their contents and release mechanisms. None of the pancreatic enzyme products are absorbed from the gastrointestinal tract in appreciable amounts, but exert their action locally in the GI tract. Pancreatic enzymes are excreted in the feces.

Author: Brandy Fouts, Pharm.D.

Pancrelipase, Pancreaze, Creon, Ultresa, Pertzye, Zenpep - Enteric-coated to minimize destruction or inactivation in gastric acid. The capsule is designed to release most enzymes at a pH greater than 5.5.

Contraindications/warnings:[7-13]

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of pancreatic enzymes exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).
- Use in caution in patients with gout due to the potential increase in uric acid levels. Consider monitoring uric acid levels in patients with hyperuricemia, gout, or renal impairment.
- There is theoretical risk of viral transmission with all pancreatic enzyme products.
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.
- Due not chew pancreatic enzyme capsules do avoid irritation of oral mucosa.

Author: Brandy Fouts, Pharm.D.

References

1. Giuliano, CA, ML Dohoorne-Smith, PB Kale-Pradhan. Pancreatic enzyme products: digesting the changes. Ann Pharmacother 2011;45:658-66.
2. Safdi M, PK Bekal, S Martin, ZA Saeed, F Burton, PP Toskes. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006;33:156-62.
3. Whitcomb DC, GA Lehman, G Vasileva, 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;105:2276-86.
4. Trapnell BC, K Maguiness, GR Graff, D Boyd, K Beckmann, S Caras. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370-7.
5. Graff GR, K Maguiness, J McNamara, R Morton, D Boyd, K Beckmann, D Bennett. Efficacy and tolerability of new formulation of pancrelipase delayed-release capsules in children aged 7 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;32(1):89-103.
6. Trapnell BC, SD Stausbaugh, MS Woo, et al. Efficacy and safety of Pancreaze for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2011;10:350-6.
7. Creon prescribing information. Abbott Laboratories. 5/2011.
8. Zenpep prescribing information. Eurand Pharmaceuticals, Inc. 7/2011.
9. Viokace prescribing information. Aptalis Pharma US, Inc. 3/2012.
10. Ultresa prescribing information. Aptalis Pharma US, Inc. 3/2012.
11. Pancrelipase prescribing information. Eurand Pharmaceuticals, Inc. 4/2010.
12. Pertzye prescribing information. Digestive Care Inc. 5/2012.
13. PANCREAZE prescribing information. Janssen Pharmaceuticals Inc. 9/2011.
14. Center for Drug Evaluation and Research. FDA Summary Review: Application 20-725. Accessed 5/15/2012 at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Author: Brandy Fouts, Pharm.D.

Appendix A:

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
2. Safdi et a 2006 DB, RCT, PC N =27	1. Creon 10: 4 capsules with meals and 2 capsules with snacks. 2. Placebo	Adults >18 years old with chronic pancreatitis and a 12-month history of pancreatic exocrine insufficiency (EPI)	2 week washout followed by a 14 day trial	<u>Mean Δ in coefficient of fat absorption (CFA) from run-in to double –blind phase:</u> Creon 10: 36.7% 95% CI (17.6-55.8) Placebo: 12.1% 95% CI (1.3, 22.9) (p=0.0185) <u>Stool frequency (# of stools)</u> Creon 10: 10.8 to 5.2 Placebo: 14.0 to 14.6 P=0.0015 <u>Daily mean fat excretion in stool (g/day)</u> Creon 10: -56.6 (95% CI -94.8,-18.2) Placebo: -11.4 (95% CI -26.7,3.9) p= 0.0181	N/A	<u>Number of subjects with at least 1 adverse event:</u> Creon 10: 3 (23%) Placebo: 5 (36%) p-value: not reported	N/A	Quality rating: Poor Study was stopped early due to slow recruitment Patients had high fat diets of at least 100g fat/day Most common side effects in patients using Creon were asthenia, cholestatic jaundice, nausea, myalgia, and tremor. The most common side effects in patients using placebo were abdominal pain, neck pain, back pain, anorexia, rectal disorder, pathological fracture, bronchitis, skin disorder, and nephrosclerosis.

3. Whitcomb 2011 MC, RCT, PC, DB n=54	• Pancrelipase: 72,000 lipase units per main meal, 36,000 lipase units per snack x 7 days with meals •Placebo x 7 days with meals	• Patients ≥ 18 years old with confirmed CP or total or partial pancreatect-omy >180 days before enrollment, and severe EPI. Severe EPI was identified by fecal fat ≥40g/day and/or CFA <80%).		<u>Mean Δ in CFA from baseline:</u> Pancrealipase: 32.1%±18.5 Placebo: 8.8%±12.5 p<0.0001 <u>Mean Δ in CNA from baseline:</u> Pancrealipase: 97.7%±82.3 Placebo: 24.4%±101 p<0.0013	N/A	<u>TEAEs:</u> Pancrelipase: 5 (20%) Placebo: 6 (20.7%) p-value: not reported	N/A	Quality rating: Fair The pancrelipase group contained a greater proportion of PS patients (36%) compared to the placebo group (17.2%). The dose of PERT that patients were using at baseline was not standard, thus some patients may have been undertreated prior to randomization. Fat content of diets may have also changed during the measurement period. Patients enrolled in this study will be entered into an open-label extension trial.
4. Trapnell 2009 DB, RCT, PC N=32	1. Creon 24,000/placebo x 5 days each 2. Placebo /Creon 24,000 x 5 days each Creon was dosed to achieve a dose of 4000 lipase units/g fat	Patients with cystic fibrosis <u>≥</u>12 years with exocrine pancreatic insufficiency.	Two 5 day sequences	<u>Least squares CFA</u> Creon: 88.6% (2.3) Placebo: 49.6% (2.3) P<0.001 <u>Least squares mean coefficient of nitrogen absorption (CNA):</u> Creon: 85.1% (1.9) Placebo: 49.9% (1.9) P<0.001	N/A	<u>Any adverse effect:</u> Creon: 14 (44%) Placebo: 20 (65%) p-value: not reported <u>Discontinue due to adverse effects</u>: Creon: 1 (3.1%) Placebo: 0 (0%) p-value: not reported	N/A	Quality rating: Fair Patients had to have been on a stable pancreatic enzyme regimen for <u>≥</u> 3 months Only 31 patients finished the entire study

5. Graff et al. 2010 MC, RCT, PC, DB, XO n=17	1. Pancrelipase x 5 days then placebo x 5 days, 2 week washout, then repeat. 2. Placebo x 5 days and then pancrelipase x 5 days, 2 week washout, then repeat. Pancrelipase 12,000 unit lipase caps were used. Target dose: lipase units/g of dietary fat intake x 5 days and then placebo.	Patients 7-11 years with CF and EPI. EPI = CFA<70% without supplementation or as human fecal elastase <50mcg/g stool in the past 12 months. Patients must have been at a stable dose of pancreatic enzyme replacement therapy for > 3 months and clinically stable (bodyweight, respiratory disease).	Two 5 day phases separated by a two week washout.	<u>Mean CFA</u>: Pancrelipase: 82.8% (77, 88.6) Placebo: 47.4% (41.6, 53.2) Difference: 35.4% (27.2, 43.6), p<0.001 <u>Mean CNA:</u> Pancrelipase: 80.3% (73.5, 87.2) Placebo: 45% (38.2, 51.8) Difference: 35.3% (25.7, 45) p<0.001	N/A	<u>TEAEs:</u> Pancrelipase: 5 (29.4%) Placebo: 9 (56.3%) p-value: not reported	N/A	Quality rating: Fair There were some discrepancies in the balance of patient characteristics between treatment groups. The treatment/placebo group was 55.6% male, and the placebo/treatment group was 87.5% male. Four patients in the treatment/placebo group were using acid-suppressing drugs compared to 0 in the alternative group. The treatment benefit observed in this trial was similar in magnitude to other clinical trials that included the same endpoint.

6. Trapnell 2011 RCT, MC, PC, DB N=40	• Pancreaze 10.5 and 31 capsules • Placebo	• Patients aged 7-60 years old with confirmed CF and CF-related exocrine pancreatic insufficiency	7 day screening phase, followed by an open label ≤14 day run-in phase, followed by a double-blind phase ranging from 4-7 days	Mean CFA (SD): Pancreaze: 86.8% (8.09) Change from baseline: -1.5 (5.9) Placebo: 56.4% (24.9) Change from baseline: -34.1 (23) p<0.001 Mean CNA (SD): Pancreaze: 82.4% (6.0) Change from baseline: 1.3 (4.7) Placebo: 57.9% (19.7) Change from baseline: -26.5 (15.3) p<0.001	N/A	Adverse effects, n (%): Any Placebo: 11 (55) Pancreaze: 4 (20) Pancreaze: 3 abdominal pain, 1 bloating, 1 vomiting Placebo: 6 abdominal pain, 3 bloating, 4 diarrhea, 3 greasy stools, 0 vomiting No serious adverse effects	N/A	Quality rating: Fair Patients were on a stable pancreatic enzyme regimen for ≥1 month prior to study. Included adult and pediatric patients.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction,
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, CGIDS = clinical global impression of disease symptoms scale , CFA coefficient of fat absorption, coefficient of nitrogen absorptio
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

.