

Pancreatic Enzyme Products: Digesting the Changes

Christopher A Giuliano, Michelle L Dehoorne-Smith, and Pramodini B Kale-Pradhan

Pancreatic enzyme products (PEPs) are commonly used in patients with exocrine pancreatic insufficiency (EPI). Common causes of EPI include cystic fibrosis, pancreatic surgery, and chronic pancreatitis. EPI can result in decreased absorption of nutrients, steatorrhea, bloating, nausea, pain, diabetes mellitus, abnormal gastric motility, and decreased weight. Maintaining adequate nutrition in patients with cystic fibrosis and EPI can be challenging, as pancreatic insufficiency can occur in 85-90% of the cases.¹ Poor nutrition in patients with cystic fibrosis may result in decreased lung function.² Patients with chronic pancreatitis or pancreatectomy and EPI may also experience nutritional concerns such as deficiencies in the fat-soluble vitamins A, D, E, and K.³ In turn, this may lead to long-term health-related issues such as osteoporosis.⁴

PEPs were exempted from the Food, Drug, and Cosmetic Act of 1938 and therefore did not require Food and Drug Administration (FDA) approval. This resulted in a plethora of PEPs, giving health-care providers the ability to choose from more than 15 PEP products. These products were available in a variety of formulations including microsphere, microcapsule, enteric-coated, and regular-release products.⁵ Differences in product design were formulated to allow for varying release of pancreatic enzymes to facilitate optimal fat absorption.

OBJECTIVE: To review the pharmacology, dosage regimens, efficacy, and safety of currently marketed pancreatic enzyme products (PEPs).

DATA SOURCES: Studies were identified by PubMed (1966-January 2011), clinicaltrials.gov, fda.gov, and *International Pharmaceutical Abstracts*. Search terms included pancreatic enzyme, lipase, Creon, Zenpep, Pancreaze, and exocrine pancreatic insufficiency (EPI).

STUDY SELECTION AND DATA EXTRACTION: All human studies evaluating the efficacy of currently approved or potential PEPs were reviewed.

DATA SYNTHESIS: PEPs are composed of porcine lipase, amylase, and protease and are used in patients with EPI secondary to cystic fibrosis, chronic pancreatitis, and pancreatectomy. In 1938, PEPs were exempted from the Food, Drug, and Cosmetic Act of 1938 and never underwent a formal Food and Drug Administration (FDA) review process. In response to reports of treatment failures during product interchange, the FDA conducted a review of available PEP products. This review found a large variability of response between the unapproved PEP products, which resulted in the FDA requiring approval of all PEP products by April 2010. The 3 delayed-release, enteric-coated PEPs currently approved by the FDA (Creon, Zenpep, and Pancreaze) have demonstrated efficacy and safety in EPI secondary to cystic fibrosis. Creon has also demonstrated safety and efficacy in EPI secondary to chronic pancreatitis and pancreatectomy. Cost difference between the 3 products is minimal. Treatment-related adverse events in clinical studies for all PEPs were less than or similar to those with placebo.

CONCLUSIONS: At this time, Creon is an appropriate first-line agent, as it has been approved for chronic pancreatitis, pancreatectomy, and cystic fibrosis.

KEY WORDS: Creon, exocrine insufficiency, pancreatic enzyme products, Pancreaze, Zenpep.

Ann Pharmacother 2011;45:658-66.

Published Online, 3 May 2011, theannals.com, DOI 10.1345/aph.1P770

Although PEPs were widely regarded as effective, patients switching between unapproved PEP of similar enzyme units experienced treatment failures.⁶ These findings prompted FDA reviews of unapproved PEPs, which found a large variability of response between the unapproved products.⁷ This resulted in a mandate by the FDA in 2004 for all PEPs to gain new drug application approval by April 2008, which was later extended to April 2010.

Creon, Zenpep, and Pancreaze are currently the only 3 products that have been FDA approved.⁸⁻¹⁰ Creon was approved in April 2009 for treatment of EPI secondary to cystic fibrosis, chronic pancreatitis, or pancreatectomy. Following Creon's approval was Zenpep in August 2009 and Pancreaze in April 2010. The latter 2 agents, however, are currently approved only for treatment of EPI secondary to cystic fibrosis, although clinical studies are being conducted for other indications. Other PEPs, including Norzyme, Pancrecarb, Viokase, Ultrase MT, Alnara, TheraCLEC, and Bucelipase alfa are currently in Phase 2 and 3 trials.

Data Sources and Selection

Studies were identified by PubMed (1966-January 2011), clinicaltrials.gov, fda.gov, and *International Pharmaceutical Abstracts*. Only human studies published in English of the FDA-approved PEPs were included. Search terms included pancreatic enzyme, lipase, Creon, Zenpep, Pancreaze, and exocrine pancreatic insufficiency (EPI). Bibliographies of recent review articles and other sources were hand-searched to identify any additional trials. Package inserts were used to add data not available in the primary literature.

Pharmacology/Toxicology

Previously unapproved PEPs contained either pancreatin (bovine-derived) or pancrelipase (porcine-derived).¹¹ Pancrelipase has 12 times the lipolytic activity of pancreatin and is the product used in all FDA-approved PEPs. Pancreatin, however, is no longer used as a result of a higher pill burden to achieve similar lipolytic activity. Pancrelipase is a combination of porcine-derived lipase, amylase, and protease. Each of the PEP formulations contains a unique combination of these 3 enzymes. Generally considered the enzyme producing the desired therapeutic effect, lipase catalyzes the breakdown of fats to monoglycerol, glycerol, and fatty acids. In addition, amylase catalyzes starch into dextrins and short chains and protease catalyzes the breakdown of proteins into peptides and amino acids. The breakdown of protein and starch in patients with EPI is generally not compromised secondary to alternative digestive pathways. These pathways include protein breakdown via acid hydrolysis in the stomach and proteolytic enzymes secreted by the brush-border and starch breakdown by amylase secreted in the saliva and brush border enzymes. Therefore, amylase and protease replacement have a lesser therapeutic effect in EPI than lipase.

Pharmacokinetics

All 3 approved products are delayed-release enteric-coated capsules and are designed to release their enzymes

at a pH of greater than 5.5.⁸⁻¹⁰ These formulations allow for optimal lipolytic activity to be achieved in the duodenum. Pancreatic enzyme products are not absorbed to an appreciable amount.

Clinical Studies

Most trials evaluating PEPs have similar methodology. Studies of patients older than 7 years were randomized, placebo-controlled trials, whereas trials with patients younger than 7 years were open-label, evaluating only safety and tolerability. All clinical trials evaluating PEP are listed in Table 1.^{10,12-16}

Diagnosis of EPI in practice and clinical studies is primarily established by a measurement of fecal elastase (<50-100 µg/g stool, depending on the trial), although other methods of both direct and indirect testing have been employed.¹⁷ Many of these methods are used infrequently; further information can be found in a review that details the differences between these tests.¹⁸ Measurement of fecal elastase is commonly used in diagnosis of EPI because it requires a single stool sample and is easy to perform. This test determines initial need for PEP but, because of its qualitative nature, cannot determine response to PEP. Response to PEP in clinical studies is determined by the coefficient of fat absorption (CFA). Measurement of CFA in clinical practice may not be feasible, as it requires a 72-hour stool collection and knowledge of fat intake. The CFA is calculated as $CFA (\%) = 100[(\text{grams fat intake} - \text{grams fat excretion}) / \text{grams fat intake}]$ and is a surrogate marker for fat absorption. Normal values for CFA are greater than 93% in children and adults and greater than 85% in infants.¹⁹ EPI in clinical studies is defined as a CFA of less than 70%.

Common secondary outcomes included the coefficient of nitrogen absorption (CNA) as well as stool frequency and consistency. The CNA is calculated as $CNA (\%) = 100[(\text{grams protein intake} - \text{grams protein excretion}) / \text{grams protein intake}]$ and determines protein absorption. No value of CNA specifically defines EPI, but the mean value in 1 trial in healthy adults was 88.1%.²⁰ All studies defined adverse events as treatment-emergent adverse events (TEAEs). TEAEs are defined as any adverse events that occurred during the intervention period except those that also occurred prior to enrollment.

CREON

Four clinical trials meeting criteria were identified and reviewed for Creon. Each study varied in treatment regimens and age groups. An open-label, single-treatment study of a targeted dosage of 8000 lipase units/kg/day evaluated the tolerability of PEP in 18 patients less than 7 years old with cystic fibrosis.¹² Patients were required to be on a

stable PEP dose without evidence of acute medical condition to be included in the study. Efficacy was assessed by comparing a spot stool fat analysis during treatment with the study PEP versus the home PEP regimen. Median patient age was 23 months. Mean study PEP was slightly higher than home PEP (7542 vs 6966 units/kg/day). No significant difference in spot stool fat was seen in treatment with study PEP versus the home PEP regimen (28.1 vs

27.9%). Fifty percent of patients experienced TEAEs such as abdominal pain, vomiting, decreased appetite, cough, diaper rash, and rhinorrhea. No patients discontinued therapy due to TEAEs. Only the diaper rash was attributed to the study drug. Limitations of this study include its open-label design and small sample size.

A randomized, double-blind, placebo-controlled, crossover trial evaluated the efficacy of PEP in 16 patients with

Table 1. Clinical Trials of PEP Products

Reference	Age	Pts.	Design	Inclusion Criteria	Exclusion Criteria	Treatment	Outcome	TEAEs
Graff (2010) ¹²	<7 y	N = 18, CF	MC, O single-arm	Stable PEP dose, FE <50 µg/g	Major surgery, fibrosing colonopathy, DIOS, HIV, immunosuppressive agents, GI tract malignancy	Creon 8000 lipase units/kg/day vs home PEP dose	Spot stool fat in new PEP vs home PEP, 28.1% vs 27.9%	50% in both groups
Graff (2010) ¹³	7-11 y	N = 16, CF	MC, DB, R, PC, cross-over	Stable PEP dose, FE <50 µg/g, stable weight	Major surgery, BMI <10%, ileus, HIV, celiac disease, or CD	Creon 4000 lipase units/g fat vs placebo	Change in CFA, 35.4% vs placebo (82.8% vs 47.4%, $p < 0.001$); change in CNA vs placebo, 35.3% (80.3% vs 45%, $p < 0.001$)	29.4% PEP vs 56.3% placebo
Trapnell (2009) ¹⁴	≥12 y	N = 32, CF	MC, DB, R, PC, cross-over	Stable PEP dose, FE <50 µg/g, stable weight or CFA <70%	Major surgery, BMI <10%, ileus, HIV, celiac disease, or CD	Creon 4000 lipase units/g fat vs placebo	Change in CFA 39% vs placebo (88.6% vs 49.6%, $p < 0.001$) Change in CNA 34.2% vs placebo (85.1% vs 49.9%, $p < 0.001$)	43.8% PEP vs 64.5% placebo
Whitcomb (2010) ¹⁵	≥18 y	N = 54, CP, PT	MC, DB, R, PC parallel group	Abnormal secretin test or FE <100 µg/g or >15 g fecal fat/day or total P	Major surgery, pseudocyst ≥4 cm, continued alcohol abuse, GI tract malignancy, acute abdomen, ileus, HIV, celiac disease, CD	Creon 72,000 lipase units/meal 36,000 lipase units/snack vs placebo	Change in CFA 19.3% vs placebo (85.6% vs 66.3%, $p < 0.001$); change in CNA 77% vs placebo (13% vs -64%, $p < 0.001$)	20% in both groups
Wooldridge (2009) ¹⁶	<7 y	N = 19, CF	MC, O, single-arm	Stable PEP dose, FE <50 µg/g BMI >25th percentile	Fibrosing colonopathy or DIOS, hyperuricemia, hepatic insufficiency, CF-related diabetes, FEV <30%, immunosuppressive medications	Zenpep dose ^a vs new titrated PEP dose	10 pts. had response to home PEP; 11 had response to new PEP	Zenpep, 33%
	≥7 y	32 CF	MC, DB, R, PC, cross-over	Stable PEP dose, FE <50 µg/g, BMI >25th percentile	Fibrosing colonopathy or DIOS, hyperuricemia, hepatic insufficiency, CF-related diabetes, FEV <30%, immunosuppressive medications	Zenpep 1000 lipase units/kg/meal then titrated vs placebo	Change in CFA 25.5% vs placebo (88.3% vs 62.8%, $p < 0.001$); change in CNA 21.5% (87.2% vs 65.7%, $p < 0.001$)	55.9% PEP vs 50% placebo
Pancreaze Trial 1 (2010) ¹⁰	≥8 y	N = 57, CF	DB, R, PC	Not published	Not published	Pancreaze 6300 units/kg/day then titrated vs placebo	Mean CFA difference, 32%	40% PEP vs 60% placebo
Pancreaze Trial 2 (2010) ¹⁰	6-30 mo	N = 16, CF	SB, R, dose-ranging	Not published	Not published	Pancreaze, 4 dosage arms (375, 750, 1125, 1500) units/kg/meal vs placebo	Not published	Not published

BMI = body mass index; CD = Crohn's disease; CF = cystic fibrosis; CFA = coefficient of fat absorption; CNA = coefficient of nitrogen absorption; CP = chronic pancreatitis; DB = double-blind; DIOS = distal ileal obstruction syndrome; FE = fecal elastase; FEV = forced expiratory volume; GI = gastrointestinal; MC = multicenter; O = observational; P = pancreatectomy; PC = placebo-controlled; PEP = pancreatic enzyme products; PT = pancreatectomy; R = randomized; SB = single-blind; TEAEs = treatment-emergent adverse events.

^aZenpep dose was patient's home PEP dose.

cystic fibrosis and EPI between the ages of 7 and 11.¹³ This trial evaluated the efficacy of 12,000-lipase unit capsules by comparing CFA values during a 5-day treatment course. Patients were required to be on a stable PEP dose without evidence of any acute medical condition. Patients were not allowed use of opioid analgesics, laxatives, antispasmodics, systemic steroids, immunosuppressive agents, or nutritional supplements containing medium-chain triglycerides. Doses were determined based on dietary fat intake at a dose of 4000 lipase units per gram of fat. A significant treatment difference of 35.4% was shown in the treatment arm versus placebo for CFA (82.8% vs 47.4%, $p < 0.001$). A similar difference of 35.3% was shown in the treatment difference of CNA (80.3% vs 45%, $p < 0.001$). TEAEs occurred in 29.4% of patients receiving PEP versus 56.3% of patients receiving placebo. These TEAEs included diarrhea, abdominal pain, nausea, vomiting, increase in blood glucose, headache, and urticaria. No patients discontinued therapy due to TEAEs. Limitations of this study included a small sample size.

Another randomized, double-blind, placebo-controlled, crossover study of 16 patients with cystic fibrosis and EPI evaluated the efficacy of 24,000 lipase unit capsules by comparing patient CFA values.¹⁴ Median patient age was 22 years. Subjects received a mean of 10,942 lipase units/kg/day. The treatment arm showed a difference in the CFA of 39% over placebo (88.6% vs 49.6%, $p < 0.001$). Likewise, a similar difference was shown in the CNA of 34.2% favoring the treatment arm (85.1% vs 49.9%, $p < 0.001$). TEAEs occurred in 43.8% of patients receiving PEP compared to 64.5% in the placebo group. These TEAEs included abdominal pain, flatulence, weight loss, headache, and cough. One patient withdrew from the trial secondary to a decrease in weight during the PEP to placebo washout period, although this was thought to be unrelated to PEP therapy. The major limitation of this study is the high dosing regimen ($>10,000$ units lipase/kg/day); this regimen is not often used in clinical practice.

The last Creon study reviewed was a double-blind, randomized, placebo-controlled, parallel trial of 54 patients with chronic pancreatitis or pancreatic surgery.¹⁵ This study evaluated the efficacy of a fixed dose of 72,000 lipase units with meals and 36,000 with snacks by comparing patient CFA values. Patients needed a CFA less than 80% or a total stool fat content of 40 g or more to be included. Additionally, the patients were not allowed to use laxatives. Median patient age was 54 years. The treatment arm showed a difference in CFA of 19.3% over placebo (85.6% vs 66.3%, $p < 0.001$), and a similar difference was shown in the CNA of 77%, favoring the treatment arm (13% vs -64%, $p < 0.001$). TEAEs were 20% in both groups. TEAEs thought to be related to treatment included abnormal feces, increased bowel movements, and loss of glucose control. No patients discontinued therapy due to

TEAEs. A large number of patients were excluded from this study and these results may not apply to patients with a lesser degree of EPI.

ZENPEP

Creon has been studied in cystic fibrosis, chronic pancreatitis, and pancreatectomy; Zenpep has been studied only in patients with cystic fibrosis. Wooldridge and colleagues reported the results of 2 trials in patients with cystic fibrosis.¹⁶ The first was an open-label trial in 19 patients younger than 7 years. Response of study PEP versus home PEP was defined as the absence of steatorrhea ($<30\%$ fecal fat on a spot fecal fat test) and signs or symptoms of malabsorption. Mean patient age was 3.9 years. Initial dosing was based on home PEP (mean 5094 lipase units/kg/day) and doses were titrated to efficacy during the treatment phase (mean 5417 lipase units/kg/day). Eleven of the 19 patients who received study PEP in the trial were classified as responders, compared to 10 of the 19 patients at the start of the study. Seventeen of the 51 TEAEs were attributed to the study drug. These included abdominal pain, steatorrhea, flatulence, vomiting, and diarrhea. No patients discontinued therapy because of TEAEs. Limitations of this study include a small sample size and its open-label design.

The second study was a randomized, double-blind, placebo-controlled, crossover trial in 34 patients 7 years of age or older (mean 15.4) that evaluated the efficacy of a titrated study PEP by evaluation of CFA.¹⁶ The initial dosage was 1000 units/kg/meal; it was titrated to efficacy based on symptoms of EPI. The mean difference in the CFA was 25.5% (88.3% vs 62.8%, $p < 0.001$), and in the CNA was 21.5% (87.2% vs 65.7%, $p < 0.001$), favoring the treatment arm. More patients in the PEP group (55.9%) experienced TEAEs compared to 50% in the placebo group, including abdominal pain, steatorrhea, flatulence, vomiting, and diarrhea. No patients discontinued therapy due to TEAEs. Limitations of this study include a small sample size.

PANCREAZE

Unlike the previous 2 products, Pancreaze clinical trial data have not been published, but the product has received approval from the FDA. Furthermore, unlike other products, clinical trial data in children (aged >30 months to <8 years) are not available. Trial information is available through the package insert.¹⁰ The first was a randomized, double-blind, placebo-controlled trial evaluating 57 patients with cystic fibrosis and EPI.¹⁰ Patients were administered 6300 lipase units/kg/day and doses were then individually titrated. Patient age ranged from 8 to 57 years. The mean difference in patient CFA values was 32%, favoring treatment over placebo. TEAEs were less common in the treat-

ment versus placebo group (40% vs 60%). These adverse events included abdominal pain, diarrhea, and flatulence.

The second study evaluating Pancreaze was randomized and single-blind, including 16 patients (age 6 to 30 months; mean 18 months) with cystic fibrosis and EPI.¹⁰ Treatment was transitioned from the patients' home dose to 375 lipase units/kg/meal for a 6-day run-in period. Patients were then randomized to receive 375, 750, 1125, or 1500 lipase units per kilogram body weight per meal for 5 days. At the end of the study, patients' overall CFA values were similar to those with their home therapy. TEAEs included diarrhea and vomiting.

Limitations

Although there are limited clinical trial data available, these data are more robust than previously available information. Most limitations are similar between studies as these 8 trials have many of the same design features. There are several confounding issues in clinical studies, such as the use of acid suppressive agents, gastric motility agents, and bile secretion modulators. Common limitations of clinical studies also include small sample sizes and relatively short follow-up periods. Coadministration of acid suppressive therapy and PEP has shown an increased amount of fat absorption secondary to decreased destruction of PEP by a decrease in gastric acid.^{21,22} Increased acidity can result in inactivation of lipase, precipitation of bile acids, and increased duodenal flow.²³ Gastric motility in patients with EPI may improve with PEP supplementation, which may result in an overcorrection of motility if use of prokinetic gastric motility agents is continued.²⁴ Increased gastric motility in patients with EPI may be related to increased amounts of undigested lipid components, which may affect CFA values. It is also possible that bile acid sequestrants decrease the efficacy of PEP by preventing bile from emulsifying fats, although no studies have evaluated this hypothesis. Although many studies had small sample sizes, all showed a positive influence of PEP compared to placebo on CFA. Due to the low incidence of conditions associated with EPI, larger studies are likely not feasible. At this time, long-term safety cannot be evaluated, as all trials lasted less than 1 month. However, unapproved PEPs have been regarded as safe when taken for longer times.

Dosage and Administration

Dosages are based on lipase units because lipase is broken down before reaching the duodenum to a greater extent than amylase or protease and other reasons previously described.²⁵⁻²⁷ Dosages are given at a fraction of the maximal normal endogenous release, as up to 140,000 units of lipase are postprandially released in adults without EPI.²⁸ Per package insert, initial doses are determined on a unit

per kilogram basis, and package insert dosing is based on recommendations from the Cystic Fibrosis Foundation guidelines (Table 2).²⁹⁻³¹ For patients receiving a previous PEP, the most practical method for switching from one PEP to another would be using a 1:1 lipase unit conversion for initial dosing and then titrating the dose to efficacy.

Adverse Effects and Drug Interactions

Common adverse events of PEPs in clinical trials included nausea, abdominal pain, vomiting, cough, frequent bowel movements, dizziness, constipation, diarrhea, early satiety, and decreases in weight. Adverse events are difficult to differentiate between symptoms of EPI and adverse events of PEPs. Of note, there are case reports of fibrosing colonopathy with higher doses of older PEP in patients with cystic fibrosis, and caution is recommended when doses exceed 2500 units/kg/meal or 10,000 units/kg/day.^{32,33} PEPs have shown to increase uric acid levels, so caution should be used in patients with gout, hyperuricemia, or renal impairment. No drug interactions have been identified to date.

Therapeutic and Economic Issues

Providers face considerable challenges when deciding which PEP to select. In the past, institutions and health-care plans may have used many PEP formulations because of the wide variability in dosage forms and variability of actual enzyme content within products. Currently, all 3 PEPs available come in a delayed-release enteric-coated dosage form but contain varying enzyme strengths. Cost differences among the 3 products are minimal. Table 3³⁴ describes the 3 products.

As a result of improved FDA standards for approved PEPs, decreased intradose and interproduct variability allows prescribers to have greater confidence in restricting product selection. Therefore, developing an interchange policy is more feasible. When converting from 1 product to another, rounding up to an increased dose may be preferred instead of rounding down, as long as the maximum mealtime and daily dosages are not exceeded. This strategy is preferred, as efficacy is based on the amount of lipase

Table 2. Pancreatic Enzyme Dosing²⁹⁻³¹

Infants (up to 12 mo)	2000-4000 lipase units per 120 mL of formula or breast milk
12 mo to <4 y ^a	Initial dose: 1000 lipase units/kg of body weight per meal, then titrate per response
>4 y and adults ^a	Initial dose: 500 lipase units/kg of body weight per meal, then titrate per response
^a Maximum dose 2500 lipase units/kg of body weight per meal (or ≤10,000 lipase units/kg of body weight per day) or <4000 lipase units/g fat ingested per day.	

that reaches the duodenum. A small percentage increase in lipase dosage will not significantly affect safety.³⁵ A potential interchange protocol is provided in Appendix I.

Patient Counseling

To ensure adequate enzyme delivery and maximum nutritional benefit, it is important that patients receive adequate counseling. PEPs should be taken with meals and snacks. It is important to advise patients to not ingest pancreatic enzymes with foods that have a pH greater than 5.5 (eg, milk, ice cream, yogurt) as this may cause premature release of pancreatic enzymes, which may, in turn, cause mucosal damage.³⁶ A list of the pH values of various foods is available at the FDA Web site.³⁷ Likewise, if the capsule is opened, it should be kept away from the nose, eyes, or other mucous membranes, as the product may cause damage to the lungs and mucosal membranes. For patients who are unable to swallow the capsule, its contents may be mixed with applesauce and given orally, as long as the contents are not crushed. The patient should be instructed to swallow the medication whole, not chew the capsule, and take it with a full glass of water. Capsules should be kept at room temperature, away from moisture and light. Patients should be advised to contact their health-care provider if itching, hives, difficulty breathing, swelling, or chest tightness occurs.

Future Trials

Future trials of approved PEPs are planned to address current limitations. Trials evaluating Creon use in EPI include one specifically investigating use of the product after pancreatic surgery.³⁸ A study evaluating Zenpep in chronic pancreatitis has recently been completed, although results have not yet been published.³⁹ Also, a Zenpep clinical trial

evaluating PEP in patients younger than 12 months with cystic fibrosis is enrolling patients.⁴⁰

Many products are currently in clinical trials, and there will likely be a significant increase in the number of available products over the course of the next few years. Products currently in Phase 3 trials include Norzyme, Pancrecarb, Viokase, Ultrase MT, and Alnara (ALTU-135).⁴¹⁻⁴⁵ A noninferiority trial comparing Norzyme versus Creon is being completed. Products currently in Phase 2 trials include TheraCLEC and Bucelipase alfa.^{46,47}

Formulary Recommendations

All 3 PEPs recently approved have shown efficacy in treatment of EPI. Efficacy is based on a lipase dosage that is high enough to ensure adequate absorption of fats. Although products are similar in price, keeping all 3 on the formulary may not be fiscally or operationally responsible. If an institution is using a limited formulary, Creon appears to be the most appropriate first-line agent, as it has been approved for chronic pancreatitis, pancreatectomy, and cystic fibrosis. Institutions may consider allowing patients to bring PEPs being used in their homes to prevent retitration to a different PEP. As other products are approved, a protocol interchange of products should be evaluated.

Summary

The 3 delayed-release, enteric-coated PEPs currently approved by the FDA (Creon, Zenpep, and Pancreaze) have demonstrated efficacy and safety in the treatment of EPI. New formulations are regulated by the FDA, which will allow for consistent enzyme unit strength in new and future PEPs. At this time, Creon appears to be the most appropriate first-line agent, as it has been approved for treatment of chronic pancreatitis, pancreatectomy, and cystic fibrosis.

Christopher A Giuliano PharmD, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, St. John Hospital and Medical Center, Detroit, MI

Michelle L Dehoorne-Smith PharmD, Manager, Patient Care Services, St. John Hospital and Medical Center

Pramodini B Kale-Pradhan PharmD, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, St. John Hospital and Medical Center

Correspondence: Dr. Kale-Pradhan, pkale@wayne.edu

Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1P770

Conflict of interest: Authors reported none

References

1. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. *Pediatr Pulmonol* 2006;41:35-49. DOI 10.1002/ppul.20286
2. Konstan MW, Butler SM, Wohl ME, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003;142:624-30. DOI S0022-3476(03)00059-310.1067/mpd.2003.152

Table 3. FDA-Approved Pancreatic Enzyme Product Enzyme Content and Price

Product	Price, per Capsule, \$ ^a	Enzyme, units		
		Lipase	Protease	Amylase
Zenpep	0.87	5,000	17,000	27,000
	1.62	10,000	34,000	55,000
	2.29	15,000	51,000	82,000
	3.30	20,000	68,000	109,000
Creon	0.97	6,000	19,000	30,000
	1.82	12,000	38,000	60,000
	3.30	24,000	76,000	120,000
Pancreaze	0.50	4,200	10,000	17,500
	1.57	10,500	25,000	43,750
	2.53	16,800	40,000	70,000
	3.15	21,000	37,000	61,000

FDA = Food and Drug Administration.

^aPrices based on average wholesale price; actual prices may vary.

3. Dutta SK, Bustin MP, Russell RM, Costa BS. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. *Ann Intern Med* 1982;97:549-52.
4. Haaber AB, Rosenfalck AM, Hansen B, Hilsted J, Larsen S. Bone mineral metabolism, bone mineral density, and body composition in patients with chronic pancreatitis and pancreatic exocrine insufficiency. *Int J Pancreatol* 2000;27:21-7. DOI 10.1385/IJGC:27:1:21
5. Krishnamurthy DM, Rabiee A, Jagannath SB, Andersen DK. Delayed release pancrelipase for treatment of pancreatic exocrine insufficiency associated with chronic pancreatitis. *Ther Clin Risk Manag* 2009;5:507-20.
6. Hendeles L, Dorf A, Stecenko A, Weinberger M. Treatment failure after substitution of generic pancrelipase capsules. Correlation with in vitro lipase activity. *JAMA* 1990;263:2459-61.
7. Food and Drug Administration. Updated questions and answers for healthcare professionals and the public: use an approved pancreatic enzyme product (PEP). <http://www.fda.gov/Drugs/DrugSafety/Postmarket-DrugSafetyInformationforPatientsandProviders/ucm204745.htm> (accessed 2010 Nov 3).
8. Product information. Creon (pancrelipase). North Chicago, IL: Abbot Products, December 2010.
9. Product information. Zenpep (pancrelipase). Milan, Italy: Eurand, December 2009.
10. Product information. Pancreaze (pancrelipase). Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc., December 2010.
11. Pankaj P. Treatment of disorders of bowel motility and water flux; antiemetics; agents used in biliary and pancreatic disease. In: Brunton LL, Lazo J, Parker KL, ed. *Goodman & Gilman's the pharmacological basis of therapeutics*. 11th ed. New York, NY: McGraw-Hill, Inc., 2006:1005-6.
12. Keller J, Aghdassi AA, Lerch MM, Mayerle JV, Luyer P. Tests of pancreatic exocrine function—clinical significance in pancreatic and non-pancreatic disorders. *Best Pract Res Clin Gastroenterol* 2009;23:425-39. DOI S1521-6918(09)00038-910.1016/j.bpg.2009.02.013
13. Chowdhury RS, Forsmark CE. Pancreatic function testing. *Aliment Pharmacol Ther* 2003;17:733-50.
14. Malabsorption. 5-Minute pediatric consult. Lippincott Williams and Wilkins. Lexi-comp (accessed 2010 Nov 3).
15. Borowitz D, Konstan M, O'Rourke A, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. *J Pediatr Pharmacol Ther* 2007;12:47-52.
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 Invest* 2010;30:351-64. DOI 110.2165/11533390-000000000-00000
17. Graff GR, Maguiness K, McNamara J, et al. Efficacy and tolerability of a 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;32:89-103. DOI S0149-2918(10)00013 510.1016/j.clinthera.2010. 01.012
18. 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;8:370-7. DOI S1569-1993(09)00122-2 10.1016/j.jcf.2009.08.008
19. Whitcomb DC, Lehman GA, Vasileva G, 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. DOI ajg2010201 10.1038/ajg.2010.201
20. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. *J Cyst Fibros* 2009;8:405-17. DOI S1569-1993(09)00096-4 10.1016/j.jcf.2009.07.006
21. Dominguez-Munoz JE, Iglesias-Garcia J, Iglesias-Rey M, Vilarino-Insua M. Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. *Gut* 2006;55:1056-7. DOI 55/7/1056-a10.1136/gut.2006.094912
22. Vecht J, Symersky T, Lamers CB, Masclee AA. Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. *J Clin Gastroenterol* 2006;40:721-5. DOI 00004836-200609000-00012
23. DiMaggio EP. Gastric acid suppression and treatment of severe exocrine pancreatic insufficiency. *Best Pract Res Clin Gastroenterol* 2001;15:477-86. DOI 10.1053/bega.2001.0195S1521691801901957
24. Vu MK, Vecht J, Eddes EH, Biemond I, Lamers CB, Masclee AA. Antroduodenal motility in chronic pancreatitis: are abnormalities related to exocrine insufficiency? *Am J Physiol Gastrointest Liver Physiol* 2000; 278:G458-66.
25. Luyer P, Brambs HJ, Ell C, et al. [1995 gastroenterology update—II]. *Med Klin (Munich)* 1996;91(suppl 1):81-8.
26. Luyer P, Go VL, DiMaggio EP. Fate of pancreatic enzymes during small intestinal aboral transit in humans. *Am J Physiol* 1986;251:G475-80.
27. Luyer P, Keller J. Pancreatic enzymes: secretion and luminal nutrient digestion in health and disease. *J Clin Gastroenterol* 1999;28:3-10.
28. Greenberger NJ. Enzymatic therapy in patients with chronic pancreatitis. *Gastroenterol Clin North Am* 1999;28:687-93.
29. 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;127:681-4. DOI S002234769500535X
30. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2002;35: 246-59.
31. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. 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;108:832-9. DOI S0002-8223(08)00179-X10.1016/j.jada.2008.02.020
32. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1997;336(18):1283-9. DOI 10.1056/NEJM199705013361803
33. Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fi-

Appendix I. Pancreatic Enzyme Substitution Protocol for Interchange of Pancreatic Enzyme Products

Pancreatic supplements for all patients will be converted to Creon.

Creon is available in capsules containing 6000, 12,000, and 24,000 units. Two different capsule sizes may be used to achieve equivalent lipase content. Doses should be rounded up, not to exceed 2500 units/kg/dose or 10,000 units/kg/day. If lipase exceeds maximum units/kg, convert to a lower lipase dosage.

Creon (units)	Pancreaze (units)
6,000	4,200
12,000	10,500
18,000	16,800
24,000	21,000
36,000	33,600
42,000	42,000
66,000	63,000
84,000	84,000
Creon (units)	Zenpep (units)
6,000	5,000
12,000	10,000
18,000	15,000
24,000	20,000
30,000	30,000
42,000	40,000
60,000	60,000
72,000	70,000

brosis: results of a case-control study. *Lancet* 1995;346:1247-51. DOI S0140-6736(95)91860-4

34. McKesson Pharmaceutical. Wholesaler pricing database. www.mckesson.com/en_us/McKesson.com/our%2BBusinesses/McKesson%2BPharmaceutical/Products%2Band%2BServices.html (accessed 2011 Apr 27).
35. Berardi RR, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: a pathophysiologic approach*, 7th ed. New York, NY: McGraw-Hill, 2008: 659-673.
36. Pancrelipase. Drugdex. Greenfield Village, CO. Thomson Micromedex, expired 2010. (accessed 2011 Jan 20).
37. Food and Drug Administration. CFSAN—bad bug book—pH values of various foods. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204745.htm> (accessed 2011 Jan 20).
38. National Institutes of Health. Creon after pancreatic surgery. www.clinicaltrials.gov/ct2/show/NCT00535756?term=Exocrine+pancreatic+insufficiency&rank=34 (accessed 2010 Dec 1).
39. National Institutes of Health. A Study of EUR-1066 in subjects with chronic pancreatitis, exocrine pancreatic insufficiency and chronic abdominal pain. www.clinicaltrials.gov/ct2/show/NCT01159119?term=zenpep&rank=1 (accessed 2010 Dec 1).
40. National Institutes of Health. A study to evaluate the mode of administration in infants less than 12 months of EUR-1008. www.clinicaltrials.gov/ct2/show/NCT01100606?term=Exocrine+pancreatic+insufficiency&rank=17 (accessed 2011 Jan 20).
41. National Institutes of Health. Clinical non-inferiority of pancreatic enzymes (Norzyme-Bergamo) compared to Creon (Solvay Pharmaceutical) in patients with exocrine pancreatic insufficiency. www.clinicaltrials.gov/ct2/show/NCT01012908?term=Exocrine+pancreatic+insufficiency&rank=19 (accessed 2011 Jan 20).
42. National Institutes of Health. Intraduodenal aspiration study to assess the bioavailability of oral pancrecarb compared to placebo control. www.clinicaltrials.gov/ct2/show/NCT00744250?term=Exocrine+pancreatic+insufficiency&rank=15 (accessed 2011 Jan 20).
43. National Institutes of Health. An open-label study to evaluate the intraduodenal delivery of enzymes from administration of VIOKASE16 in exocrine pancreatic insufficiency (EPI). www.clinicaltrials.gov/ct2/show/NCT00559052?term=Exocrine+pancreatic+insufficiency&rank=11 (accessed 2011 Jan 20).
44. National Institutes of Health. Efficacy and safety of ULTRASE MT20 in improving the coefficient of fat absorption (CFA%) in children with cystic fibrosis (CF) and pancreatic insufficiency (PI). www.clinicaltrials.gov/ct2/show/NCT00513682?term=Exocrine+pancreatic+insufficiency&rank=10 (accessed 2011 Jan 20).
45. National Institutes of Health. ALTU-135 efficacy trial in patients with cystic fibrosis-related exocrine pancreatic insufficiency (DIGEST). www.clinicaltrials.gov/ct2/show/NCT00449878?term=Exocrine+pancreatic+insufficiency&rank=2 (accessed 2010 Dec 1).
46. National Institutes of Health. Efficacy of bucelipase alfa (BSSL) in patients with cystic fibrosis and pancreatic insufficiency. www.clinicaltrials.gov/ct2/show/NCT00743483?term=Exocrine+pancreatic+insufficiency&rank=7 (accessed 2010 Dec 1).
47. National Institutes of Health. Randomized double-blind placebo cross-over study to evaluate safety/efficacy of two doses in CP patients with EPI. www.clinicaltrials.gov/ct2/show/NCT00788593?term=Exocrine+pancreatic+insufficiency&rank=13 (accessed 2010 Dec 1).

Productos de Enzimas Pancreáticas; Digiriendo los Cambios

CA Giuliano, ML Dehoorne-Smith, y PB Kale-Pradhan

Ann Pharmacother 2011;45:658-66.

EXTRACTO

OBJETIVO: Revisar la farmacología, regímenes de dosificación, eficacia y seguridad de los productos disponibles en el mercado que contienen enzimas pancreáticas (PEPs).

FUENTE DE DATOS: Los estudios revisados se identificaron mediante el uso de los sistemas de información PubMed (1966-enero, 2011), clinicaltrials.gov, fda.gov, y la base de datos *Abstractos Farmacéuticos Internacionales*. Los términos incluidos en la búsqueda de información fueron enzima pancreática, lipasa, Creon, Zenpep, Pancreaze, e insuficiencia pancreática exocrina (EPI).

SELECCIÓN DE ESTUDIOS Y OBTENCIÓN DE LA INFORMACIÓN: Se revisaron todos los estudios en humanos que evaluaron la eficacia de los PEPs, actualmente aprobados y los que potencialmente se aprobarán en el futuro.

SÍNTESIS DE LOS DATOS: Los PEPs son medicamentos que se componen de lipasa porcina, amilasa, y proteasa. Se utilizan en pacientes con insuficiencia pancreática exocrina secundaria a fibrosis quística, pancreatitis crónica y pancreatocistitis. En el 1983, los PEPs fueron exentos de la Ley de Drogas, Alimentos y Cosméticos y nunca tuvieron un proceso de evaluación a través de la Administración de Drogas y Alimentos (FDA). Debido a que han existido informes sobre fallos terapéuticos cuando se hace un intercambio entre los productos, el FDA llevó a cabo una revisión de los productos actualmente disponibles. En esta revisión se encontró una variabilidad grande en la respuesta de los PEPs no aprobados. Esto llevó al FDA a requerir la aprobación de los productos que contienen enzimas pancreáticas para abril de 2010. Los 3 productos actualmente aprobados por el FDA que son de liberación retardada, con capa entérica (Creon, Zenpep, Pancreaze), han demostrado ser eficaces y seguros en insuficiencia pancreática exocrina secundaria a fibrosis quística. Creon también ha demostrado ser seguro y eficaz en insuficiencia pancreática exocrina secundaria a pancreatitis crónica y pancreatocistitis. La diferencia en costo entre estos 3 productos es mínima. Las reacciones adversas relacionadas con el tratamiento con PEPs en los estudios clínicos fueron menores o similares a los encontrados con placebo.

CONCLUSIONES: Actualmente, Creon es un agente adecuado de primera línea, ya que su uso ha sido aprobado para pancreatitis crónica, pancreatocistitis y fibrosis quística.

Traducido por Mirza Martinez

Les Enzymes Pancréatiques: Digérer les Changements

CA Giuliano, ML Dehoorne-Smith, et PB Kale-Pradhan

Ann Pharmacother 2011;45:658-66.

RÉSUMÉ

OBJECTIF: Revoir la pharmacologie, les posologies, l'efficacité et l'innocuité des produits d'enzymes pancréatiques.

SOURCE DE DONNÉES: Les études ont été identifiées par le biais de MEDLINE (1966-janvier 2011), clinicaltrials.gov, fda.gov, et de l'*International Pharmaceutical Résumé*. Les termes de recherche incluaient les produits d'enzymes pancréatiques, lipase, Creon, Zenpep, Pancreaze, et insuffisance pancréatique exocrine.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Toutes les études effectuées chez les humains évaluant l'efficacité des produits présentement approuvés ou en voie de l'être ont été revues.

SYNTHÈSE DES DONNÉES: Les produits d'enzymes pancréatiques sont composés de lipase porcine, d'amylase et de protéase et sont utilisés chez les patients souffrant d'insuffisance pancréatique exocrine secondaire à la fibrose kystique, de pancréatite chronique, et à la suite d'une pancréatectomie. En 1938, les produits d'enzymes pancréatiques ont été exemptés de la Nourriture, Drogue, et Cosmétique Loi de 1938 et n'ont jamais subi une revue formelle de la FDA. En réponse à des rapports antérieurs témoignant de leurs échecs de traitement lorsque substitués, la FDA a effectué une revue des produits d'enzymes pancréatiques disponibles sur le marché. Cette revue a mis en relief la grande variabilité dans la réponse au traitement entre les produits d'enzymes pancréatiques non approuvés ce qui a conduit la FDA à requérir l'approbation de tous les produits d'enzymes pancréatiques pour Avril 2010. Les 3 produits d'enzymes pancréatiques à enrobage entérique et libération retardée présentement approuvés par la FDA (Creon, Zenpep, et Pancreaze) ont démontré leur efficacité et leur

innocuité pour le traitement de l'insuffisance pancréatique exocrine secondaire à la fibrose kystique. Creona également démontré son efficacité et son innocuité dans le traitement de l'insuffisance pancréatique exocrine secondaire à une pancréatite chronique et à la suite d'une pancréatectomie. La différence de coûts entre les 3 produits est minime. Les effets secondaires reliés au traitement et rapportés dans les études pour tous les produits d'enzymes pancréatiques étaient moindres ou similaires au placebo.

CONCLUSIONS: À l'heure actuelle, Creon est un agent de première ligne approprié puisque qu'il a été approuvé pour le traitement de la pancréatite chronique, la fibrose kystique, et à la suite d'une pancréatectomie.

Traduit par Chantal Guévremont

NEW EDITION

MEDICAL ABBREVIATIONS

32,000 Conveniences at the Expense
of Communications and Safety

15th Edition • By Neil M. Davis

424 pp / Paperbound / ISBN 0-931431-15-9 / 2011 / \$28.95



The 15th edition includes a “do not use” list of dangerous abbreviations in addition to the 32,000 meanings for the abbreviations, acronyms, and symbols. The book also contains a cross-referenced list of 3,400 generic and trade drug names. Each copy includes a single-user access license for the web version of the book for use in all of your devices. This license is valid for 12 months from the date of initial log-in.

Essential to medical professionals for order interpretation, data entry, unit dose cart filling, and prescription interpretation. A must to ensure patient safety and reduce medication errors.

Harvey Whitney Books Company
PO Box 42696 Cincinnati OH 45242-0696
Order Toll-Free: 877-742-7631
hwbooks.com