

Pancreatic Enzyme Products

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A recent Food and Drug Administration regulation has resulted in the availability of 3 new standardized pancreatic enzyme products with proven short-term efficacy and safety (Creon[®], Pancreaze[®], and Zenpep[®]). They comply with modern chemistry, manufacturing, and control criteria, including predictable amounts of enzyme content. However, they differ in available strengths, are not designated by Food and Drug Administration as therapeutically equivalent, and are not interchangeable by pharmacists without previous approval of the prescriber.

New Products

RECENTLY, FOOD AND DRUG ADMINISTRATION (FDA) approved 3 oral delayed-release pancreatic enzyme products (PEPs), Creon[®], Pancreaze[®], and Zenpep[®], for replacement therapy of exocrine pancreatic insufficiency (EPI).^{1–3} All 3 are microencapsulated formulations of pancrelipase extracted from hog pancreatic glands. They differ in enzyme content and available strengths (Table 1). They are not designated by FDA as therapeutic equivalents and, therefore, are not interchangeable by pharmacists without previous approval of the prescriber.⁴

Pancrelipase contains lipase, which catalyzes the hydrolysis of fats to monoglyceride, glycerol, and fatty acids; protease, which converts proteins into peptides and amino acids; and, amylase, which converts starches into dextrins and short-chain sugars such as maltose and maltotriose.^{1–3} The primary action of these formulations is in the duodenum and proximal small intestine.^{1–3}

They are indicated for the treatment of EPI due to cystic fibrosis (CF) or “other conditions.” Creon contains the specific additional approval for treatment of EPI in patients with chronic pancreatitis or those who have had a pancreatic resection.¹

Regulatory History

Since some PEPs were available before passage of the 1937 Pure Food and Drug Act, drug companies have been allowed to manufacture and sell PEPs without previous FDA approval.⁵ Most of these products were marketed without being tested in humans.

In the 1970s, McNeil Laboratories developed Pancrease, the first microencapsulated formulation that resisted acid

inactivation in the stomach and increased fat absorption.^{6–8} The beads were coated with a material that dissolved at a pH >5.5, thus releasing active enzymes near the site of action. A number of other products subsequently became available, but they differed in enzyme content, ability to resist acid inactivation, and the pH at which the coating dissolved and released the enzymes.⁹ Anabolic, Inc. manufactured and sold a “generic equivalent” to the original Pancrease, but pharmacist substitution of this product resulted in treatment failures in patients with CF.¹⁰ The coating on the beads did not resist acid inactivation (ie, it did not have a true enteric coating), and all of the lipase was destroyed within an hour of being exposed to simulated gastric juice.¹⁰ Subsequently, the product was taken off the market. At that time, the United States Pharmacopeia (USP) did not have an upper limit of enzyme content or test for resisting stomach acid inactivation. The products had to contain at least 90% of what was stated on the label but could contain any amount above this minimum; some contained 200% or more.⁹

FDA convened a workshop in 1992 to determine what study designs should be required to determine the efficacy and safety of PEPs,¹¹ but no agency action followed this meeting.

In 1994, case reports of fibrosing colonopathy began to appear and were temporally associated with the introduction of high-potency microencapsulated enzymes.^{12–14} These products were not tested for safety and efficacy in patients who required PEPs. As a result, the U.S. Cystic Fibrosis Foundation and FDA convened a consensus conference in March, 1995 to discuss risks and treatment of colonopathy in patients with CF. Subsequently, the higher potency products were taken off the market, and a maximum dose of 2,500 lipase units/kg/meal was recommended.¹⁵ It is still unclear what was the exact cause of the strictures. A methacrylic acid

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TABLE 1. FOOD AND DRUG ADMINISTRATION APPROVED ORAL DELAYED RELEASE PANCRELIPASE CAPSULES

Brand name (mfg)	Lipase	Protease	Amylase
Creon [®]	6,000	19,000	30,000
(Abbott Laboratories)	12,000	38,000	60,000
	24,000	76,000	120,000
Pancreaze [®]	4,200	10,000	17,500
(Ortho-McNeil-Janssen	10,500	25,000	43,750
Pharmaceuticals, Inc.)	16,800	40,000	70,000
	21,000	37,000	61,000
Zenpep [®]	5,000	17,000	27,000
(Eurand Pharmaceuticals)	10,000	34,000	55,000
	15,000	51,000	82,000
	20,000	68,000	109,000

Adapted from Food and Drug Administration Electronic Orange Book.⁴ Values are given in United States Pharmacopeia units.

copolymer in the enteric coating of some products was suspected¹⁶ but was not confirmed in a case-control study.¹⁷

Fortunately, case reports of enzyme-associated colono-
pathy have been rare since the warnings issued by the Cystic
Fibrosis Foundation.

In both the July 1991 and April 1995 Federal Register
Notices related to the withdrawal of over-the-counter PEPs,
FDA noted that it considered all EPI drug products to be new
drugs for which approved applications would be required
for marketing.^{18,19} However, it was not until April 28, 2004
that FDA actually issued notice that they were going to re-
quire a new drug application for PEPs; if manufacturers did
not have approval by 2008, they would no longer be able to
manufacture the products.²⁰ Subsequently, this deadline was
extended to April 28, 2010. In the interim, a few generic
companies manufactured and sold branded generics (eg,
Lipram[®], Pangestyme[®]) promoted to pharmacists to be
substituted for products such as Creon, Ultrase MT[®], and
Pancrease MT[®]. *In-vitro* studies conducted by manufacturers
of the brand-name products indicated that some of these
newer products varied in content and ability to withstand
exposure to simulated gastric fluid and could not be bio-
equivalent generic products.^{21,22} In some instances, products
were inactivated in simulated gastric fluid (pH 1.2) and in
other instances, the beads did not dissolve at pH 6 or higher.
Efficacy of these products in patients with EPI was never
tested.

Criteria for FDA Approval

In order to obtain FDA approval, the 3 companies of
approved products had to submit a new drug application
that contained information on the chemistry, manufacturing,
and control methods, as well as the results of clinical stud-
ies.²³ Of note, the FDA requires that the product actually
contain the same amount of enzyme as indicated on the label
and that bioactivity must be shown to correlate with the
stated potency.²³ This is in contrast to the USP criteria,
which, for example, allows a lipase content between 90% and
160% of the labeled amount. Before the new FDA standards,
overfilling ranged from 7% to 47% in PEPs with a 10–12
month shelf-life.²⁴ Currently, the FDA does not allow prod-
ucts to meet the antiquated USP standards.²³ This is why, for
example, the new Creon formulation is labeled as containing

6,000 units of lipase (its actual content), whereas the older
formulation was labeled as 5,000 units of lipase.

All 3 of the approved products were tested in patients
with CF.^{1–3} Also, Creon was tested in patients with chronic
pancreatitis or after pancreatectomy.¹ The degree of fat
malabsorption in the study patients and study designs dif-
fered among the 3 products and so it is not possible to
make cross-product comparisons. It is noteworthy, however,
that coefficient of fat absorption (CFA), the endpoint re-
quired by FDA, has inconsistent precision in patients with
CF,²⁵ but to date no better objective alternative has been
validated. In the largest study of its kind, PEP dose did not
correlate well with growth or patient-reported gastrointesti-
nal symptoms.²⁶

Creon

Two randomized, double-blind, placebo-controlled,
crossover studies were conducted with Creon in 49 patients,
ages 7 to 43 years, with EPI due to CF. In the first study,
patients were ages 12 to 43 years and in the second study,
they were 7 to 11 years. In each study, patients were ran-
domized to receive Creon at a dose of 4,000 lipase units/gm
of fat ingested/day or matching placebo for 5–6 days of
treatment followed by a 3–14 day washout and subsequent
crossover to the alternate treatment for an additional 5–6
days. The CFA was determined after patients consumed a
100 gram fat/day diet and had a marker-to-marker stool
collection at the end of each treatment. In the first study, the
mean [95% confidence interval (CI)] difference in CFA was
39 (34, 47) percentage points ($P=0.001$).²⁷ In the second
study, the mean (95% CI) difference was 35 (27, 44) per-
centage points. Results for the coefficient of nitrogen ab-
sorption were similar. In the third study, Creon was
compared with placebo in a randomized, double-blind,
placebo-controlled, parallel group study of 54 adult patients,
ages 32 to 75 years, with EPI due to chronic pancreatitis or
resulting from pancreatectomy. In this study, patients re-
ceived placebo for 5 days (run-in period) followed by ran-
domization to either Creon or matching placebo for 7 days.
Only patients with CFA <80% in the run-in period were
randomized to the double-blind period. The lipase dose of
Creon was 72,000 units/meal (3 meals/day) and 36,000
units/snack (2 snacks/day) during a high-fat diet. The
treatment difference between the 2 groups was 21 (14, 28)
percentage points ($P=0.0001$).

Pancreaze

The New Drug Application for this product contained 2
short-term studies in patients with CF with EPI.² The first was
a randomized, double-blind, placebo-controlled withdrawal
study of 40 patients, ages 8 to 57 years. The dose of Pancreaze
was titrated individually during a 14-day run-in period, up to
2,500 units/kg/meal lipase, and then patients were treated
with active drug or matching placebo for 7 days in a rando-
mized withdrawal design. Only patients with a CFA of >80%
during the run-in period on active drug were randomized into
the double-blind period. The point estimate for the treatment
difference (95% CI) was 33(25,40) percentage points. The sec-
ond study was a randomized, investigator-blinded, parallel
group dose ranging study of 17 patients ages 6–30 months with
EPI due to CF. All patients were transitioned from their usual

dose of PEP to 375 units/kg/meal of Pancreaze during a 6-day run-in period, which served as the baseline period. Then, they were randomized to receive either 375, 750, 1,125, or 1,500 lipase units/kg/meal for 5 days. CFA was measured at the end of the run-in period and at the end of the randomized treatment period. The mean CFA was 92%, 91%, 80%, and 91%, respectively. The change in CFA% was 1 to 2 percentage points, and higher doses did not increase CFA% more than lower doses, that is, the dose-response curve was flat. These are the only dose-ranging data available for porcine PEP. They bring into question either the current published guidelines of titrating dosage or the use of CFA as an endpoint to measure PEP efficacy.

Zenpep

Zenpep was evaluated in 2 studies of 53 patients with CF, ages 1 to 23 years, with EPI. The first study was a randomized, double-blind, placebo-controlled, crossover study of 34 patients, ages 7 to 23 years.²⁸ Patients were treated with a starting dose of 1,000 lipase units/kg/meal, with dose increases at the investigator's discretion. Subjects were then randomized to receive Zenpep or matching placebo for 6–7 days of treatment followed by crossover to the alternate treatment for an additional 6–7 days. CFA was determined after subjects were on a 100 g fat/day diet and had a 72-hour stool collection. The mean difference (95% CI) in CFA between Zenpep and placebo was 26 (19, 32) percentage points. The second study was an open-label, uncontrolled study of 19 subjects ages 1 to 6 years (mean age 4 years) with EPI due to CF.³ This study compared a spot fecal fat measurement during therapy with the previous commercial product that the subject was taking and after oral administration of Zenpep capsules. Zenpep was administered in individually titrated doses (mean lipase dose 5,700 units/Kg/d) for 14 days. There was no wash-out period. Overall, subjects showed a similar control of fat absorption on Zenpep as their previous regimen (numbers not provided in manufacturer's information).

Common to studies of all 3 products was the fact that subanalyses indicated that subjects with the lowest off-enzyme CFA showed the greatest difference between placebo and active drug in crossover-design studies. Also, there were no age- or gender-related differences in outcomes, but the sample sizes were very small.

Adverse effects are difficult to interpret, as the studies were of limited duration and most were symptoms of EPI. Generally, adverse effects were more frequent during placebo treatment than with active enzyme. There were no cases of fibrosing colonopathy reported in the pivotal studies, and it is unclear whether uric acid excretion was measured in any of them. Hyperuricemia, constipation, oral mucosal irritation, or allergic reactions were not reported during the pivotal trials.

Products Currently Under FDA Review

Ultrase MT Capsules (Axcen Pharma US, Inc.) was not approved by FDA by the April 28, 2010 deadline and can no longer be manufactured until FDA approval is received. Apparently, there were chemistry, manufacturing, and control issues with the product. According to Axcen's letter to prescribers, FDA did not request that new clinical studies be conducted.²⁹

Liprotamase (Eli Lilly and Co.) is currently under review by FDA. It is a novel formulation of biotechnology derived lipase and protease and amylase, crystallized to provide stability at extremes of pH. In an open-label, 12-month study of CF subjects >7 years with EPI, height and weight increased steadily in patients during the years of active growth while taking 1 or more capsules containing 32,500 lipase units with each meal and with 2 snacks each day.³⁰

Discussion

FDA regulation of PEPs is long overdue but clearly beneficial. The requirement to meet more stringent *in-vitro* criteria than required by USP will prevent treatment failures or adverse effects as a result of variation in enzyme content, stability in stomach acid, and/or release in the duodenum. The 3 FDA-approved products are all new formulations. Even Creon and Pancreaze are different formulations than previous products with the same or similar name and might perform differently when patients are switched to the new products. None of these products have been proved therapeutically equivalent to one another, and they are not interchangeable by pharmacists without previous approval of the prescriber.

Perhaps a downside to the new regulation is that generic formulations are not likely to become available in the near future, which will keep the cost of therapy from decreasing. FDA's position is that PEPs currently are not likely to be appropriate for an abbreviated new drug application (as a generic), as there is no analytical tool available to demonstrate that the active ingredients from 2 different manufacturers are the same.²³

In summary, the new FDA regulations have resulted in the availability of standardized products with proven short-term efficacy and safety. These new products comply with modern chemistry, manufacturing, and control criteria and provide predictable amounts of enzyme content.

Author Disclosure Statement

Dr. Hendeles served as an expert witness on behalf of Solvay in a lawsuit in 2004 and on behalf of Axcen in 2009. Dr. Drucy Borowitz was on the CF Foundation-Alnara Scientific Advisory Committee, and her employer, University at Buffalo Pediatric Associates, was paid for her work as the international principal investigator and consultant for studies of liprotamase (now owned by Eli Lilly and Company). She has also served as a consultant to Solvay Pharmaceuticals (now Abbott).

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