



## **ZENPEP®: HELPS FUEL NUTRITIONAL HEALTH\* FOR PATIENTS WITH EXOCRINE PANCREATIC INSUFFICIENCY**

**Z**ENPEP® (pancrelipase) Delayed-Release Capsules is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF) or other conditions.<sup>1</sup>

Jose M. Nieto, D.O., F.A.C.P., of Borland Groover Clinic's Advanced Therapeutic Endoscopy Center, has prescribed ZENPEP since it first came out in 2009. He was previously on the clinical faculty at Florida Hospital Cancer Institute where he was involved in the development of the pancreatic disease and cancer program. Dr. Nieto states: "My practice is advanced endoscopy, so I deal with a significant amount of patients who have pancreatic disease and pancreatic insufficiency, not just from chronic pancreatitis but from other medical conditions that can cause pancreatic insufficiency. I started prescribing ZENPEP when it first came out on the market, and as with any medication, I kept careful tabs on how patients tolerated it."

\*ZENPEP helps fuel patients' nutritional health, as defined by improvement in the absorption of essential nutrients from foods such as fats, proteins, carbohydrates, and certain vitamins.<sup>2</sup>

In a randomized, double-blind, placebo-controlled, multicenter cross-over study, patients with EPI due to CF (ages 7 to 23 years) were given a high-fat diet and following a 6-9 day dose titration/stabilization period, were randomized to treatment with either ZENPEP or placebo for one week. Following an open-label normalization period, patients

were crossed over to the alternative treatment. The primary efficacy endpoint was the change in the mean coefficient of fat absorption (CFA) between ZENPEP and placebo, which was measured from the 72-hour stool sample collected during each inpatient hospitalization period. The use of enzymes other than ZENPEP and drugs affecting gastric pH or motility were not allowed during the trial.

Those patients treated with ZENPEP compared to placebo had significantly higher mean CFA (88.3% vs. 62.8%, respectively; primary endpoint) and CNA (87.2% vs. 65.7%, respectively; secondary endpoint) (both  $p < 0.001$ ). In addition, 16 out of 32 (50%) patients had a CFA  $> 90\%$  when treated with ZENPEP, and 29 out of 32 (90.6%) patients had a CFA  $> 80\%$  when treated with ZENPEP ( $\geq 85\%$  represents near-normal CFA values in patients with EPI due to CF).<sup>2</sup> A secondary endpoint of the study showed that 100% of patients maintained or improved their level of EPI symptom control. Data was derived from daily patient/guardian diaries; assessments were subjective and represent the mean number of abdominal pain, bloating and flatulence occurrences per day and the mean stool frequency and characteristics from the same patients during treatment with ZENPEP or placebo.<sup>2</sup>

"I have a significant number of patients on ZENPEP," reports Dr. Nieto, "and ZENPEP is generally well-tolerated." The most common adverse events ( $\geq 6\%$  of patients treated with ZENPEP) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety, and constipation.<sup>1</sup>

## ZENPEP Patient Support Program

Dr. Nieto notes, "I would like to highlight the patient programs offered by Aptalis Pharma US, Inc. As a prescribing physician, one of the biggest factors we have to deal with is how much the treatment will cost the patient and whether their insurance is going to cover it. Aptalis provides patients with assistance programs that can make ZENPEP affordable for many patients."

Eligible patients who choose to participate in the ZENPEP Patient Support Program receive a patient savings card for prescriptions of ZENPEP, nutritional supplements, refill reminders and patient education materials. Eligible patients can receive:

- Up to \$50 off their ZENPEP prescriptions
- Free vitamins with each ZENPEP refill: Designed for patients who have trouble absorbing the fat-soluble vitamins A, D, E, and K
  - Available in chewable tablets and softgels.
  - Highly absorbable, antioxidant-rich nutritional supplements containing vitamins A, D, E, and K.<sup>3†</sup>
  - Levels of vitamins found in program offerings may be too high or inappropriate for some patients.
  - Healthcare professionals should base their selection of vitamin type, formulation, and dosage on an individual patient's specific nutritional needs or deficiencies.
- Educational information about EPI and treatment

Patients can enroll in this program online at [www.ZENPEPsupport.com](http://www.ZENPEPsupport.com) or through Starter Kits available from your Aptalis Sales Representative. Restrictions apply. Please see

[www.ZENPEPsupport.com](http://www.ZENPEPsupport.com) for full eligibility requirements.

<sup>†</sup>This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent disease.

### Important Safety Information

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of ZENPEP exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)
- To avoid irritation of oral mucosa, do not chew ZENPEP or retain in the mouth
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia
- There is theoretical risk of viral transmission with all pancreatic enzyme products, including ZENPEP
- Rarely, patients taking pancreatic enzyme products with different

formulations of the same active ingredient (pancrelipase) have experienced severe allergic reactions, including anaphylaxis, asthma, hives, and pruritus

- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin
- The most common adverse events ( $\geq 6\%$  of patients treated with ZENPEP) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety, and constipation
- ZENPEP is not interchangeable with any other pancrelipase product

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### References:

1. ZENPEP [package insert]. Eurand Pharmaceuticals, Inc., Yardley, PA; July 2011
2. 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;8:405-417.
3. AquADEKS Product Information. <http://www.yasoo products.com/aquadeks/supplementfacts.html#>. UIGbv45wYy. Accessed October 19, 2012.

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**ZENPEP® (pancrelipase) delayed release capsules**  
**Initial U.S. Approval: 2009**

**Brief Summary of Prescribing Information** (for Full Prescribing Information and Medication Guide, refer to US Package Insert)

**1 INDICATIONS AND USAGE**

ZENPEP® (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Fibrosing Colonopathy**

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually with use over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. *Doses* of pancreatic enzyme products exceeding 6000 lipase units/kg of body weight per meal have been associated with colonic strictures in children less than 12 years of age. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. It is generally recommended, unless clinically indicated, that enzyme doses should be less than 2,500 lipase units/kg of body weight per meal (or less than 10,000 lipase units/kg of body weight per day) or less than 4,000 lipase units/g fat ingested per day [see *Dosage and Administration* (2.1) in the full prescribing information].

Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Patients receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

**5.2 Potential for Irritation to Oral Mucosa**

Care should be taken to ensure that no drug is retained in the mouth. ZENPEP should not be crushed or chewed or mixed in foods having a pH greater than 4.5. These actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss or enzyme activity [see *Dosage and Administration* (2.2) and *Patient Counseling Information* (17.1) in the full prescribing information]. For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents added to a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce. The ZENPEP-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

**5.3 Potential for Risk of Hyperuricemia**

Caution should be exercised when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia. Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.

**5.4 Potential Viral Exposure from the Product Source**

ZENPEP is sourced from pancreatic tissue from swine used for food consumption. Although the risk that ZENPEP will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

**5.5 Allergic Reactions**

Caution should be exercised when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported with other pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase). The risks and benefits of continued ZENPEP treatment in patients with severe allergy should be taken into consideration with the overall clinical needs of the patient.

**6 ADVERSE REACTIONS**

The most serious adverse reactions reported with different pancreatic enzyme products of the same active ingredient (pancrelipase) include fibrosing colonopathy, hyperuricemia and allergic reactions [see *Warnings and Precautions* (5) in the full prescribing information].

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The short-term safety of ZENPEP was assessed in two clinical trials conducted in 53 patients, ages 1 to 23 years, with exocrine pancreatic insufficiency (EPI) due to CF. In both studies, ZENPEP was administered in doses of approximately 5,000 lipase units per kilogram per day, for lengths of treatment ranging from 19 to 42 days.

The population was nearly evenly distributed in gender, and approximately 96% of patients were Caucasian.

Study 1 was a randomized, double-blind, placebo-controlled, 2-treatment, crossover study of 34 patients, ages 7 to 23 years, with EPI due to CF. In this study, patients were randomized to receive ZENPEP at individually titrated doses (not to exceed 2,500 lipase units per kilogram per meal) or matching placebo for 6 to 7 days of treatment, followed by crossover to the alternate treatment for an additional 6 to 7 days. The mean exposure to ZENPEP during this study, including titration period and open label transition, was 30 days.

The incidence of adverse events (regardless of causality) was similar during double blind ZENPEP treatment (56%) and placebo treatment (50%). The most common adverse events reported during the study were gastrointestinal complaints, which were reported more commonly during placebo treatment (41%) than during ZENPEP treatment (32%), and headache, which was reported more commonly during ZENPEP treatment (15%) than during placebo treatment (0). The type and incidence of adverse events were similar in children (7-11 years), adolescents (12-16 years), and adults (greater than 18 years).

Because clinical trials are conducted under controlled conditions, the observed adverse event rates may not reflect the rates observed in clinical practice.

Table 1 enumerates treatment-emergent adverse events that occurred in at least 2 patients (greater than or equal to 6%) treated with either ZENPEP or placebo in Study 1. Adverse events were classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology.

**Table 1: Treatment-Emergent Adverse Events Occurring in at least 2 Patients (greater than or equal to 6%) During Treatment Period and Crossover Treatment Period of the Placebo-Controlled, Crossover Clinical Study of ZENPEP (Study 1)**

MedDRA Primary System Organ Class Preferred Term	ZENPEP (N=34) %	Placebo (N=32) %
<b>Gastrointestinal Disorders</b>		
Abdominal pain	6 (18%)	9 (28%)
Flatulence	2 (6%)	3 (9%)
<b>Nervous System Disorders</b>		
Headache	5 (15%)	0
<b>Injury, Poisoning and Procedural Complications</b>		
Contusion	2 (6%)	0
<b>Investigations</b>		
Weight decreased	2 (6%)	2 (6%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	2 (6%)	0
<b>General Disorders and Administration Site Conditions</b>		
Early Satiety	2 (6%)	0

Study 2 was an open-label, uncontrolled study of 19 patients, ages 1 to 6 years, with EPI due to CF. After a 4-14 days screening period on the current PEP, patients in Study 2 received ZENPEP at individually titrated doses ranging between 2,300 and 10,000 lipase units per kg body weight per day, with a mean of approximately 5000 lipase units per kg body weight per day (not to exceed 2,500 lipase units per kilogram per meal) for 14 days. There was no comparator treatment, and adverse events were collected on patient diary entries and at each study visit.

The most commonly reported adverse events were gastrointestinal, including abdominal pain and steatorrhea, and were similar in type and frequency to those reported in the double-blind, placebo-controlled trial (Study 1).

**6.2 Postmarketing Experience**

Postmarketing data for ZENPEP have been available since 2009. The following adverse reactions were reported postapproval. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most commonly reported adverse events are gastrointestinal disorders (including abdominal distension, abdominal pain, diarrhea, flatulence, constipation and nausea) and skin disorders (including pruritus, urticaria, and rash).

In patients at risk for abnormal blood glucose levels glycemic control may be affected by administration of pancreatic enzyme replacement therapy. Consideration should be given to additional glucose monitoring in these patients.

Delayed- and immediate-release pancreatic enzyme products with different formulations of the same active ingredient (pancrelipase) have been used for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis and other conditions, such as chronic pancreatitis. The long-term safety profile of these products has been described in the medical literature. The most serious adverse events include fibrosing colonopathy, distal intestinal obstruction syndrome (DIOS), recurrence of pre-existing carcinoma, and severe allergic reactions including anaphylaxis, asthma, hives, and pruritus.

In general, pancreatic enzyme products have a well defined and favorable risk-benefit profile in exocrine pancreatic insufficiency.

## 7 DRUG INTERACTIONS

No drug interactions have been identified. No formal interaction studies have been conducted.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Teratogenic effects

Pregnancy Category C: Animal reproduction studies have not been conducted with pancrelipase. It is also not known whether pancrelipase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ZENPEP should be given to a pregnant woman only if clearly needed. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a pregnant woman with exocrine pancreatic insufficiency. Adequate caloric intake during pregnancy is important for normal maternal weight gain and fetal growth. Reduced maternal weight gain and malnutrition can be associated with adverse pregnancy outcomes.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZENPEP is administered to a nursing woman. The risk and benefit of pancrelipase should be considered in the context of the need to provide adequate nutritional support to a nursing mother with exocrine pancreatic insufficiency.

### 8.4 Pediatric Use

The short-term safety and effectiveness of ZENPEP were assessed in 2 clinical studies in pediatric patients, ages 1 to 17 years, with EPI due to CF.

Study 1 was a randomized, double-blind, placebo-controlled, crossover study in 34 patients 26 of whom were children, including 8 children aged 7 to 11 years, and 18 adolescents aged 12 to 17 patients. The safety and efficacy in pediatric patients in this study were similar to adult patients [see *Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information*].

Study 2 was an open-label, single arm study in 19 patients, ages 1 to 6 years, with EPI due to CF. When patient regimen was switched from their usual PEP regimen to ZENPEP at similar doses, patients showed similar control of their clinical symptoms.

The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis has been described in the medical literature and through clinical experience.

Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences [see *Dosage and Administration (2.1) in the full prescribing information*]. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy and colonic strictures in children less than 12 years of age [see *Warnings and Precautions (5.1) in the full prescribing information*].

### 8.5 Geriatric Use

Clinical studies of ZENPEP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

## 10 OVERDOSAGE

In Study 1, a 10 year-old patient was administered a dose of 10,856 lipase units per kg body weight of ZENPEP for a period of one day. The patient did not experience any adverse events as a result of the dose increase, nor did this patient experience any adverse events during a 44-day follow-up period. No abnormalities from analyses of safety labs (chemistry, hematology, urinalysis or uric acid) were noted.

Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures [see *Dosage and Administration (2.1) and Warnings and Precautions (5.1) in the full prescribing information*]. High doses of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia, and should be used with caution in patients with a history of hyperuricemia, gout, or renal impairment [see *Warnings and Precautions (5.3) in the full prescribing information*].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed.

ZENPEP® is subject of US Patent No. 7,658,918.

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