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TREATMENT OF EXOCRINE PANCREATIC INSUFFICIENCY:

Aptalis Pharma's™ ZENPEP® (pancrelipase) Offers Flexible Dosing Options

Exocrine pancreatic insufficiency (EPI) is a common sequelae of cystic fibrosis, chronic pancreatitis, pancreatic duct obstruction, and pancreatic surgery/resection resulting in insufficient levels of digestive enzymes.[1]

Challenges in Diagnosing and Treating EPI

Patients with EPI untreated or undertreated, will present with serious consequences such as maldigestion and malnutrition. The diagnosis of EPI is largely a clinical diagnosis but may require a multi-faceted approach including evaluation of signs and symptoms, direct (e.g., secretin-cerulein) or indirect (e.g., fecal fat) assessment of impaired enzyme and digestive function, and in some cases, evaluation of structural signs of chronic pancreatic disease[1,2]. There are additional challenges in determining who requires pancreatic enzyme replacement therapy (PERT) and how to treat these individuals. David Whitcomb, M.D., PhD, a leader in pancreas research, describes the challenges associated with PERT: "The CF patient, the individual with CP, and patients with other disease, may have inflammation and scarring of the pancreas. The problem is that pancreatic inflammation, pancreatic fibrosis and pancreatic insufficiency are not biologically equivalent processes. You probably can't predict the extent of insufficiency by measuring inflammation or fibrosis," explains Whitcomb. "The structure and function relationship is not linear."

Whitcomb, Chief of the Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, continues: "Regardless of what the pancreas looks like, 15 percent of CF patients with CP won't require replacement therapy because they retain enough exocrine pancreatic function to digest the nutrients they consume. And it is often difficult to predict which CP patients have EPI – even though the numbers are as high as 50-60 percent." Complicating the picture further, he adds: "With chronic pancreatitis it's a problem of a gradual loss of pancreatic exocrine function over time, until the ability to deliver the necessary amount of pancreatic digestive enzymes is lost. But you can't tell how far along it is by using structural measures such as CT scan or MRI." As result of this gradual loss of function the diagnosis of EPI may take years.

Dr. Whitcomb offers a number of tips to faciliate assessment of maldigestion:

- Steatorrhea is a sign, not a diagnostic criteria for pancreatic exocrine failure. While it is often associated with end-stage chronic pancreatitis, steatorrhea may be absent in patients with borderline EPI and a low fat diet, or it may be present in patients with consumption of undigestible lipids who have intestinal disease, or in those who are taking lipase-blocking agents.
- In symptomatic patients, with pancreatic disease and signs of maldigestion (steatorrhea, bloating, diarrhea or micronutrient or protein deficiencies) an empirical trial of an adequate dose of PERT may be used to test whether the deficiencies or symptoms dissipate.
- Pay attention to nutrition. Evaluate the patient's weight, absorption of vitamins (especially fat soluble), and protein status.

Treating Effectively with a PERT

Timing is everything. "It is so important that medications are synchronized," says Whitcomb. "For instance, if a proton pump

inhibitor is required, it should be taken 30 minutes before a meal, then the enzyme at the beginning or during the meal." With an insulin-dependent diabetic, there needs to be special attention to sync the delivery of insulin with enzyme, he adds. "If the effects of insulin precede the absorption of digested food because the PERT dose was too small or poorly timed, then the patient will become hypoglycemic. The diabetic population generally needs higher doses of enzymes with a consistent, balanced meal."

ZENPEP® (pancrelipase) is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of EPI due to CF or other conditions[3]. The efficacy, safety and tolerability of ZENPEP® were evaluated in two multicenter studies of patients with CF: a randomized, double-blind, placebo-controlled crossover trial in patients ≥ 7 years of age (N=34) and a supplemental open-label study in children < 7 years of age (N=17)[3,4]. In the randomized trial, ZENPEP® treatment resulted in clinically significant improvements in coefficients of fat (CFA) and nitrogen absorption (CNA), and reduced the incidence of malabsorption symptoms. In the supplemental trial, patients switched to ZENPEP® from a previous PERT maintained or improved control of their EPI symptoms (secondary endpoint). The most commonly reported adverse events occurring in >2 patients treated with Zenpep® during double-blind treatment were abdominal pain, flatulence, headache, contusion, weight decreased, cough, and early satiety.[3]

ZENPEP® is available in six FDA-approved dosage strengths, providing dosing flexibility for both practitioner and patient. The ability to prescribe in more precise dosing can aid in delivering an accurate dose while reducing the number of capsules taken with each meal for some patients. With approval earlier this year of new 3000 USP lipase unit and 25,000 USP lipase unit formulations, **Aptalis Pharma™** now manufactures **ZENPEP®** in both the highest and lowest doses currently approved by FDA.[3]

"A few years ago there was wide variability in the content and quality of various products sold as PERT. Now the physician can be confident that when they order a pancreatic enzyme, the patient will get exactly what they ordered," says Whitcomb. "So any change in signs and symptoms can be considered a medical issue rather than a potential problem with the product that the patient received from their pharmacy."

Ancillary Nutritional Treatments

In addition to PERT, vitamins and other supplements are important components in the management of EPI. A randomized controlled trial investigated dietary counseling and commercial dietary supplementation in undernourished patients receiving pancreatic enzyme replacement therapy (PERT).[5] "Adequate nutritional management together with PERT has the potential to improve nutritional status and maldigestion," according to the study's authors.[5]

Important Safety Information

Fibrosing colonopathy is a rare serious adverse reaction associated with high-dose use of pancreatic enzyme replacement products and most commonly reported in pediatric patients with CF.[3] Exercise caution when doses of ZENPEP® exceed 2500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).[3] To avoid irritation of oral mucosa or inactivation of enzymes, do not chew ZENPEP® capsules or beads or retain in the mouth.[3] Exercise caution when prescribing ZENPEP® to patients with gout, renal impairment, or hyperuricemia or when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.[3] There is theoretical risk of viral transmission with all pancreatic enzyme products, including ZENPEP®. The most common adverse events (>6% of patients treated with ZENPEP®) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety and contusion.[3]

For more information about ZENPEP®, please see accompanying full prescribing information or visit our website at www.aptalispharma.com.

Trademarks are owned by their respective companies.

References:

1. Hammer HF. Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes. *Digestive Diseases* 2010;28:339-343.
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5. Ockenga J. Importance of nutritional management in diseases with exocrine pancreatic insufficiency. *Hepato-Pancreato-Biliary Association (Oxford). 2009* December;11(Suppl 3):11–15.

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) %
Gastrointestinal Disorders		
Abdominal pain	*6 (18%)*	*9 (28%)*
Flatulence	2 (6%)	3 (9%)
Nervous System Disorders		
Headache	5 (15%)	0
Injury, Poisoning and Procedural Complications		
Contusion	2 (6%)	0
Investigations		
Weight decreased	2 (6%)	2 (6%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2 (6%)	0
General Disorders and Administration Site Conditions		
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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