HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZENPEP safely and effectively. See full prescribing information for ZENPEP.

ZENPEP® (pancrelipase) delayed-release capsules, for oral use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ZENPEP® is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients. (1)

DOSAGE AND ADMINISTRATION

Important Dosing Information (2.1)

- ZENPEP is a mixture of enzymes including lipases, proteases, and amylases and dosing is based on lipase units. Dosing scheme based on actual body weight or fat ingestion.
- Individualize the dosage based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.
- Do not exceed 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in adult and pediatric patients greater than 12 months of age without further investigation. (5.1)
- The total daily dosage in adult and pediatric patients greater than 12 months of age should reflect approximately three meals plus two or three snacks per day. With each snack, administer approximately half the prescribed dose for a meal.
- Do not substitute other pancreatic enzyme products for ZENPEP. When switching from another pancreatic enzyme product to ZENPEP, monitor patients for clinical symptoms of exocrine pancreatic insufficiency and titrate the dosage as needed.

Recommended Dosage (2.2)

Adult and Pediatric Patients Greater than 12 Months: The recommended initial starting dosage is:

- 500 lipase units/kg/meal for adult and pediatric patients 4 years of age and older.
- 1,000 lipase units/kg/meal for pediatric patients greater than 12 months of age to less than 4 years of age.

- Titrate the dosage to 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day. Higher dosages may be administered if documented effective by fecal fat measures or improvement in malabsorption.

Pediatric Patients Birth to 12 Months: The recommended dosage is 3,000 lipase units (one capsule) per 120 mL of formula or per breastfeeding.

Preparation and Administration Instructions (2.3)

- Swallow capsules whole. For patients unable to swallow intact capsule(s), the capsule contents may be sprinkled on soft acidic food (e.g., applesauce, bananas, pears).
- Do not crush or chew ZENPEP capsules or capsule contents.
- Consume sufficient liquids to ensure complete swallowing of ZENPEP. (5.2)
- See the full prescribing information for additional information on administering to pediatric patients birth to 12 months. (2.3)

DOSAGE FORM AND STRENGTHS

Delayed-Release Capsules (3):

- 3,000 USP units of lipase; 10,000 USP units of protease; and 14,000 USP units of amylase
- 5,000 USP units of lipase; 17,000 USP units of protease; and 24,000 USP units of amylase
- 10,000 USP units of lipase; 32,000 USP units of protease; and 42,000 USP units of amylase
- 15,000 USP units of lipase; 47,000 USP units of protease; and 63,000 USP units of amylase
- 20,000 USP units of lipase; 63,000 USP units of protease; and 84,000 USP units of amylase
- 25,000 USP units of lipase; 79,000 USP units of protease; and 105,000 USP units of amylase
- 40,000 USP units of lipase; 126,000 USP units of protease; and 168,000 USP units of amylase
- 60,000 USP units of lipase; 189,600 USP units of protease; and 252,600 USP units of amylase

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Fibrosing Colonopathy: Associated with high doses, usually over prolonged use and in pediatric patients with cystic fibrosis. Colonic stricture reported in pediatric patients less than 12 years of age with dosages exceeding 6,000 lipase units/kg/meal. Monitor during treatment for progression of preexisting disease. Do not exceed the recommended dosage, unless clinically indicated. (2.1, 5.1)
- Irritation of the Oral Mucosa: May occur due to loss of protective enteric coating on the capsule contents. (2.3, 5.2)
- Hyperuricemia: Reported with high dosages, consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia. (5.3)
- Risk of Viral Transmission: The presence of porcine viruses that might infect humans cannot be definitely excluded. (5.4)
- Hypersensitivity Reactions: Monitor patients with known reactions to proteins of porcine origin. If symptoms occur, initiate appropriate medical management; consider the risks and benefits of continued treatment. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (≥6%) are: headache, contusion, cough, and early satiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics, Inc at 1-833-AIM2KNO (1-833-246-2566) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2025

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

ZENPEP® is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients.

2. DOSAGE AND ADMINISTRATION

2.1. Important Dosing Information

ZENPEP is a mixture of enzymes including lipases, proteases, and amylases. ZENPEP dosing is based on lipase units.

- Use either an actual body weight or fat ingestion-based dosing scheme.
- Start at the lowest recommended dosage and individualize the dosage based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Changes in dosage may require an adjustment period of several days.
- Do not exceed 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in adult and pediatric patients greater than 12 months of age without further investigation *[see Warnings and Precautions (5.1)]*.
- The total daily dosage in adult and pediatric patients greater than 12 months of age should reflect approximately three meals plus two or three snacks per day. With each snack, administer approximately half the prescribed ZENPEP dose for a meal.
- Do not substitute other pancreatic enzyme products for ZENPEP. When switching from another pancreatic enzyme product to ZENPEP, monitor patients for clinical symptoms of exocrine pancreatic insufficiency and titrate the dosage as needed.

2.2. Recommended Dosage

Adult and Pediatric Patients Greater than 12 Months of Age

The recommended oral initial starting dosage is:

- 500 lipase units/kg/meal for adult and pediatric patients 4 years of age and older.
- 1,000 lipase units/kg/meal for pediatric patients greater than 12 months of age to less than 4 years of age.

If signs and symptoms of malabsorption persist, increase the dosage. Titrate to either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or less than 4,000 lipase units/grams of fat ingested/day. Higher dosages may be administered if they are documented to be effective by fecal fat measures or an improvement in signs or symptoms of malabsorption including measures of nutritional status.

Pediatric Patients Birth to 12 Months of Age

The recommended oral dosage is 3,000 lipase units per 120 mL of formula or per breast-feeding.

2.3. Preparation and Administration Instructions

Instruct adult and pediatric patients greater than 12 months of age, or their caregivers, of the following:

- Take ZENPEP during meals or snacks. If a dose is missed, take the next dose with the next meal or snack.
- Swallow capsules whole.
- For patients who are unable to swallow intact capsules, carefully open the capsules and sprinkle the entire contents on a small amount of acidic soft food with a pH of 4.5 or less (e.g., commercially available preparations of applesauce, bananas, or pears). Consume the entire mixture immediately.
- Do not crush or chew ZENPEP capsules or capsule contents.
- Consume sufficient liquids (water or juice) to ensure complete swallowing of ZENPEP *[see Warnings and Precautions (5.2)]*.

Instruct caregivers of pediatric patients birth to 12 months of age of the following:

- Immediately prior to each breast-feeding session or each administration of 120 mL of formula, carefully open one ZENPEP capsule (containing 3,000 USP units of lipase) and administer the entire contents using one of the following two methods:
  - Sprinkle on a small amount of acidic soft food with a pH of 4.5 or less (e.g., commercially available preparations of applesauce, bananas or pears) being careful not to crush the capsule contents. The entire mixture should be given to the infant immediately.
  - Sprinkle the capsule contents directly into the infant's mouth.
- Immediately administer additional breast milk or formula after ZENPEP to ensure complete swallowing of the capsule contents.
- Do not mix the ZENPEP capsule contents directly into a bottle of breast milk or formula.
- Do not crush ZENPEP capsule contents, and visually inspect the infant's mouth to ensure that no drug is retained in the mouth *[see Warnings and Precautions (5.2)]*.
- If a dose is missed, administer the next dose with the next feeding.

3. DOSAGE FORMS AND STRENGTHS

Delayed-release capsules are available in the following strengths:

- 3,000 USP units of lipase; 10,000 USP units of protease; and 14,000 USP units of amylase in a two piece hypromellose capsule with a white opaque cap and white opaque body, and red imprint with "APTALIS 3"
- 5,000 USP units of lipase; 17,000 USP units of protease; and 24,000 USP units of amylase in a two piece hypromellose capsule with a white opaque cap and white opaque body, and blue imprint with "APTALIS 5"
- 10,000 USP units of lipase; 32,000 USP units of protease; and 42,000 USP units of amylase in a two-piece hypromellose capsule with a yellow opaque cap and white opaque body, and blue imprint with "APTALIS 10"
- 15,000 USP units of lipase; 47,000 USP units of protease; and 63,000 USP units of amylase in a two-piece hypromellose capsule with a red opaque cap and white opaque body, and blue imprint with "APTALIS 15"

- 20,000 USP units of lipase; 63,000 USP units of protease; and 84,000 USP units of amylase in a two-piece hypromellose capsule with a green opaque cap and white opaque body, and blue imprint with “APTALIS 20”
- 25,000 USP units of lipase; 79,000 USP units of protease; and 105,000 USP units of amylase in a two-piece hypromellose capsule with a blue opaque cap and white opaque body, and blue imprint with “APTALIS 25”
- 40,000 USP units of lipase; 126,000 USP units of protease; and 168,000 USP units of amylase in a two-piece hypromellose capsule with an orange opaque cap and white opaque body, and blue imprint with “APTALIS 40”
- 60,000 USP units of lipase; 189,600 USP units of protease; 252,600 USP units of amylase. Capsules have a powder blue opaque cap with two black stripes and white opaque body, black imprint with “APTALIS 60”

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with pancreatic enzyme products. Fibrosing colonopathy is a rare serious adverse reaction initially described in association with use of high-dose pancreatic enzyme products, usually with use over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. Pancreatic enzyme products exceeding 6,000 lipase units/kg/meal have been associated with colonic stricture, a complication of fibrosing colonopathy, in pediatric patients less than 12 years of age. The underlying mechanism of fibrosing colonopathy remains unknown.

If there is a history of fibrosing colonopathy, monitor patients during treatment with ZENPEP because some patients may be at risk of progressing to colonic stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. Do not exceed the recommended dosage of either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in adult and pediatric patients greater than 12 months of age without further investigation. Higher dosages may be administered if they are documented to be effective by fecal fat measures or an improvement in signs or symptoms of malabsorption including measures of nutritional status. Patients receiving dosages higher than 6,000 lipase units/kg/meal should be frequently monitored for symptoms of fibrosing colonopathy and the dosage decreased or titrated downward to a lower range if clinically appropriate *[see Dosage and Administration (2.1)]*.

5.2. Irritation of the Oral Mucosa

Crushing or chewing ZENPEP capsules or mixing the capsule contents in foods having a pH greater than 4.5 can disrupt the protective enteric coating on the capsule contents and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Instruct the patient or caregiver of the following:

- Swallow capsules whole. For patients who cannot swallow the capsules whole, the capsules can be opened, and the contents sprinkled on a small amount of acidic soft food with a pH of 4.5 or less (e.g., commercially available preparations of applesauce, bananas or pears).
- Do not crush or chew ZENPEP capsules or capsule contents.
- Consume sufficient liquids (juice, water, breast milk, or formula) immediately following administration of ZENPEP to ensure complete swallowing.
- Visually inspect the mouth of pediatric patients less than 12 months of age and of patients who are unable to swallow intact capsules to ensure no drug is retained in the mouth and irritation of the oral mucosa has not occurred *[see Dosage and Administration (2.3)]*.

5.3. Hyperuricemia

Pancreatic enzyme products contain purines that may increase blood uric acid levels. High dosages have been associated with hyperuricosuria and hyperuricemia *[see Overdosage (10)]*.
Consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia during treatment with ZENPEP.

5.4. Risk of Viral Transmission

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. Hypersensitivity Reactions

Severe hypersensitivity reactions including anaphylaxis, asthma, hives, and pruritus have been reported with pancreatic enzyme products *[see Adverse Reactions (6.2)]*. If symptoms occur, initiate appropriate medical management.

Monitor patients with a known hypersensitivity reaction to proteins of porcine origin for hypersensitivity reactions during treatment with ZENPEP. The risks and benefits of continued ZENPEP treatment in patients with severe hypersensitivity reactions should be taken into consideration with the overall clinical needs of the patient.

6. ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are described elsewhere in the labeling:

- Fibrosing Colonopathy *[see Warnings and Precautions (5.1)]*
- Irritation of the Oral Mucosa *[see Warnings and Precautions (5.2)]*
- Hyperuricemia *[see Warnings and Precautions (5.3)]*
- Risk of Viral Transmission *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*

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 data described below reflect exposure to ZENPEP in 53 adult and pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis in two clinical trials conducted *[see Clinical Studies (14)]*. In both trials, ZENPEP was administered at dosages of approximately 5,000 lipase units/kg/day for 19 to 42 days.

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 34 adult and pediatric patients, aged 7 to 23 years. Adverse reactions that were reported in at least 2 ZENPEP-treated patients (greater than or equal to 6%) and at a higher rate than in placebo-treated patients in Study 1 are shown in Table 1.

Table 1: Adverse Reactions* in a Clinical Trial of Adult and Pediatric Patients 7 Years of Age and Older with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis (Study 1)

Adverse Reaction	ZENPEP N=34 n (%)	Placebo N=32 n (%)
Headache	5 (15%)	0
Contusion	2 (6%)	0
Cough	2 (6%)	0
Early Satiety	2 (6%)	0

* Reported in at least 2 ZENPEP-treated patients (greater than or equal to 6%) and at a higher rate than placebo-treated patients.

Study 2 was an open-label, uncontrolled study of ZENPEP in 19 pediatric patients aged 1 to 6 years. The most commonly reported adverse reactions were gastrointestinal, including abdominal pain and steatorrhea.

The type and incidence of adverse reactions in Studies 1 and 2 were similar between pediatric patients and adults.

6.2. Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZENPEP or other pancreatic enzyme products. 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.

Eye Disorders
- blurred vision

Gastrointestinal Disorders
- fibrosing colonopathy and distal intestinal obstruction syndrome
- abdominal distension, abdominal pain, diarrhea, flatulence, constipation, and nausea

Immune System Disorders
- anaphylaxis, asthma, hives and pruritis

Investigations
- asymptomatic elevations of liver enzymes

Musculoskeletal System
- myalgia, muscle spasm

Skin and Subcutaneous Tissue Disorders
- urticaria and rash

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Published data from case reports with pancrelipase use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Pancrelipase is minimally absorbed systematically; therefore, maternal use is not expected to result in fetal exposure to the drug. Animal reproduction studies have not been conducted with pancrelipase.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2. Lactation

Risk Summary

There are no data on the presence of pancrelipase in either human or animal milk, the effects on the breastfed infant or the effects on milk production. Pancrelipase is minimally absorbed systemically following oral administration, therefore maternal use is not expected to result in clinically relevant exposure of breastfed infants to the drug. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZENPEP and any potential adverse effects on the breastfed infant from ZENPEP or from the underlying maternal conditions.

8.4. Pediatric Use

The safety and effectiveness of ZENPEP for the treatment of exocrine pancreatic insufficiency have been established in pediatric patients.

Use of ZENPEP for this indication is supported by an adequate and well-controlled trial in adult and pediatric patients 7 to 17 years of age (Study 1) along with supportive data from an open-label, single arm study in 19 pediatric patients 1 to 6 years of age (Study 2). Both study populations consisted of patients with exocrine pancreatic insufficiency due to cystic fibrosis. The safety in pediatric patients in Studies 1 and 2 were similar to that observed in adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Dosages exceeding 6,000 lipase units/kg/meal have been reported postmarketing to be associated with fibrosing colonopathy and colonic strictures in pediatric patients less than 12 years of age. If there is a history of fibrosing colonopathy, monitor patients during treatment with ZENPEP because some patients may be at risk of progressing to stricture formation. Do not exceed the recommended dosage of either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in pediatric patients greater than 12 months of age without further investigation. *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Crushing or chewing ZENPEP capsules or mixing the capsule contents in foods having a pH greater than 4.5 can disrupt the protective enteric coating on the capsule contents and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity. Instruct the patient or caregiver of the following: consume sufficient liquids (juice, water, breast milk, or formula) to ensure complete swallowing, and visually inspect the mouth of pediatric patients less than 12 months of age to ensure that no drug is retained in the mouth and irritation of the oral mucosa has not occurred *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

8.5. Geriatric Use

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

10. OVERDOSAGE

Chronic high dosages of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures *[see Warnings and Precautions (5.1)]*. High dosages of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia *[see Warnings and Precautions (5.3)]*.

11. DESCRIPTION

Pancrelipase is a pancreatic enzyme product consisting of a mixture of enzymes including lipases, proteases, and amylases, and is an extract derived from porcine pancreatic glands. The enteric-coated pellets in ZENPEP are formulated to release pancreatic enzymes at an approximate pH of 5.5 or greater.

ZENPEP (pancrelipase) delayed-release capsule for oral administration, include a two-piece shell containing light brown-colored enteric-coated pellets (1.8 to 1.9mm for 3,000 and 5,000 USP units of lipase, 2.2 to 2.5 mm for 10,000, 15,000, 20,000, 25,000, 40,000 and 60,000 USP units of lipase) and are available as follows:

3,000 USP units of lipase; 10,000 USP units of protease; and 14,000 USP units of amylase; delayed-release capsules have a white opaque cap and a white opaque body with imprint “APTALIS 3”. The shells contain carnauba wax or talc, carrageenan, hypromellose, potassium chloride, titanium oxide, and water. The colorant of the printed ink is red iron oxide.

5,000 USP units of lipase; 17,000 USP units of protease; and 24,000 USP units of amylase; delayed-release capsules have a white opaque cap and a white opaque body with imprint “APTALIS 5”. The

shells contain carnauba wax or talc, carrageenan, hypromellose, potassium chloride, titanium oxide, and water. The colorant of the printed ink is FD&C Blue 2.

10,000 USP units of lipase; 32,000 USP units of protease; and 42,000 USP units of amylase; delayed-release capsules have a yellow opaque cap and a white opaque body with imprint “APTALIS 10”. The shells contain carnauba wax or talc, carrageenan, hypromellose, potassium chloride, titanium oxide, water and yellow ferric oxide. The colorant of the printed ink is FD&C Blue 2.

15,000 USP units of lipase; 47,000 USP units of protease; and 63,000 USP units of amylase; delayed-release capsules have a red opaque cap and a white opaque body with imprint “APTALIS 15”. The shells contain carnauba wax or talc, carrageenan, hypromellose, potassium chloride, red ferric oxide, titanium oxide, and water. The colorant of the printed ink is FD&C Blue 2.

20,000 USP units of lipase; 63,000 USP units of protease; and 84,000 USP units of amylase; delayed-release capsules have a green opaque cap and a white opaque body with imprint “APTALIS 20”. The shells contain carnauba wax or talc, carrageenan, FD&C Blue #2, hypromellose, potassium chloride, titanium oxide, water, and yellow ferric oxide. The colorant of the printed ink is FD&C Blue 2.

25,000 USP units of lipase; 79,000 USP units of protease; and 105,000 USP units of amylase; delayed-release capsules have a blue opaque cap and a white opaque body with imprint “APTALIS 25”. The shells contain carnauba wax or talc, carrageenan, FD&C Blue #2, hypromellose, potassium chloride, titanium oxide, and water. The colorant of the printed ink is FD&C Blue 2.

40,000 USP units of lipase; 126,000 USP units of protease; and 168,000 USP units of amylase; delayed-release capsules have an orange opaque cap and white opaque body, printed with “APTALIS 40”. The shells contain FD&C Yellow #6, hypromellose, and titanium oxide. The colorant of the printed ink is FD&C Blue 2.

60,000 USP units of lipase; 189,600 USP units of protease; 252,600 USP units of amylase. Capsules have a powder blue opaque cap with two black stripes and white opaque body, printed with "APTALIS 60" The shells contain FD&C Blue #1, hypromellose, and titanium oxide. The colorant of the printed ink is black iron oxide.

ZENPEP (pancrelipase) delayed-release capsules include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc, and triethyl citrate.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Pancreatic enzyme products contain a mixture of lipases, proteases, and amylases that catalyze the hydrolysis of fats to monoglycerides, glycerol, and free fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

12.2. Pharmacodynamics

For patients consuming a high fat diet in the clinical trials, the coefficient of fat absorption (CFA) was higher in patients who received ZENPEP compared to the placebo treatment group, indicating improved fat absorption *[see Clinical Studies (14)]*.

12.3. Pharmacokinetics

Following oral administration, the lipases, proteases, and amylases released from ZENPEP are not absorbed from the gastrointestinal tract in appreciable amounts.

Drug Interactions

The lipases, proteases, and amylases of ZENPEP are not substrates of CYP enzymes or transporters. CYP enzymes or transporters mediated drug interactions are not expected.

14. CLINICAL STUDIES

Adult and Pediatric Patients 7 Years of Age and Older

Study 1 was a randomized, double-blind, placebo-controlled, crossover study of 34 patients, aged 7 to 23 years, with exocrine pancreatic insufficiency due to cystic fibrosis. The final analysis population was limited to 32 patients, who completed both double-blind treatment periods, and were included in the efficacy analysis population. Patients were randomized to receive ZENPEP 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 mean dosage during the controlled treatment periods ranged from a mean dose of 3,900 lipase units/kg/day to 5,700 lipase units/kg/day. All patients consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the treatment period. The population was nearly evenly distributed in biological sex, and approximately 96% of patients were White.

Coefficient of Fat Absorption Endpoint and Results
The primary efficacy endpoint was the mean difference in the coefficient of fat absorption (CFA) between ZENPEP and placebo treatment. The CFA was determined by a 72-hour stool collection during both treatments, when both fat excretion and fat ingestion were measured. Each patient's CFA during placebo treatment was used as their no-treatment CFA value.

Mean CFA was 88% with ZENPEP treatment compared to 63% with placebo treatment. The mean difference in CFA was 26 percentage points in favor of ZENPEP treatment with 95% Confidence Interval of (19, 32) and $p<0.001$.

Subgroup analyses of the CFA results showed that mean change in CFA was greater in patients with lower no-treatment (placebo) CFA values than in patients with higher no-treatment (placebo) CFA values. There were similar responses to ZENPEP by age and biological sex.

Pediatric Patients 1 to 6 Years of Age

Study 2 was an open-label, uncontrolled study of 19 pediatric patients, aged 1 to 6 years (mean age 4 years), with exocrine pancreatic insufficiency due to cystic fibrosis. Approximately half of the patients were aged 1 to 3 years. Study 2 compared a measurement of fat malabsorption, spot fecal fat testing,

before (while receiving therapy with another pancreatic enzyme product) and after oral administration of ZENPEP capsules with each meal or snack.

After a 4 to 14 day screening period during which patients remained on their current pancreatic enzyme product, patients were switched to ZENPEP at individually titrated dosages ranging between 2,300 and 10,000 lipase units/kg/day (not to exceed 2,500 lipase units/kg/meal) for 14 days. The mean ZENPEP dosage was approximately 5,000 lipase unit/kg/day. There was no wash-out period. Overall, patients showed similar control of fat malabsorption by spot fecal fat testing when switched from their current pancreatic enzyme product to ZENPEP treatment at a similar dosage.

16. HOW SUPPLIED/STORAGE AND HANDLING

ZENPEP (pancrelipase) delayed-release capsules containing light, brown-colored delayed-release pancrelipase are supplied as follows:

Strength	**Description**	**Supplied As**	**NDC Number**
3,000 USP units of lipase; 10,000 USP units of protease; 14,000 units of amylase	two-piece hypromellose capsule with white opaque cap and white body with a red radial print and printed with "APTALIS 3"	Bottles of 100	73562-113-01
5,000 USP units of lipase; 17,000 USP units of protease; 24,000 units of amylase	two-piece hypromellose capsule with a white opaque cap and white body with a blue radial print and printed with "APTALIS 5"	Bottles of 100	73562-115-01
10,000 USP units of lipase; 32,000 units of protease; 42,000 units of amylase	two-piece hypromellose capsule with a yellow opaque cap and white body with a blue radial print and printed with "APTALIS 10"	Bottles of 100	73562-110-01
15,000 USP units of lipase; 47,000 units of protease; 63,000 units of amylase	two-piece hypromellose capsule with a red opaque cap and white body with a blue radial print and printed with "APTALIS 15"	Bottles of 100	73562-111-01
20,000 USP units of lipase; 63,000 units of protease; 84,000 units of amylase	two-piece hypromellose capsule with a green opaque cap and white body with a blue radial print and printed with "APTALIS 20"	Bottles of 100	73562-112-01
25,000 USP units of lipase; 79,000 units of protease; 105,000 units of amylase	two-piece hypromellose capsule with a blue opaque cap and white body with a blue radial print and printed with "APTALIS 25"	Bottles of 100	73562-116-01
40,000 USP units of lipase; 126,000 units of protease; 168,000 units of amylase	two-piece hypromellose capsule with an orange opaque cap and white body with a blue radial print and printed with "APTALIS 40"	Bottles of 100	73562-114-01
60,000 USP units of lipase; 189,600 units of protease; 252,600 units of amylase	two-piece hypromellose capsule with powder blue opaque cap with two black stripes and white body with a black radial print and printed with "APTALIS 60"	Bottles of 100	73562-117-01

Storage and Handling

Original container:
Store at room temperature, 20°C to 25°C (68°F to 77°F) and protect from moisture. Brief excursions permitted to 15°C to 40°C (59°F to 104°F) for 24 hours. *After opening, keep bottle tightly closed between uses to protect from moisture.*

Zenpep is supplied in bottles containing a desiccant.

Repackaged HDPE container:
Dispense in tight container (USP). Store at up to 30°C (86°F) for up to 6 months and protect from moisture. Brief excursions permitted to 15°C to 40°C (59°F to 104°F) for up to 30 days. Protect from moisture. *After opening, keep bottle tightly closed between uses to protect from moisture*.

17. PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Fibrosing Colonopathy

Advise the patient or caregiver that fibrosing colonopathy has been reported with high dosages of pancreatic enzyme products, usually with use over a prolonged period of time and in pediatric patients with cystic fibrosis. Colonic stricture has been reported in pediatric patients less than 12 years of age. Advise patients and caregivers that if signs and symptoms of colon stricture formation occur (e.g., stomach area (abdominal) pain, bloating, trouble passing stool (constipation), nausea, vomiting, diarrhea) to immediately contact their healthcare provider *[see Warnings and Precautions (5.1)]*.

Hyperuricemia

Advise the patient or caregiver that hyperuricemia may occur in patients with gout or renal impairment and to contact the healthcare provider if they experience pain, stiffness, redness or swelling of their joints *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions

Inform the patient or caregiver that severe hypersensitivity reactions, including anaphylaxis asthma, hives, and pruritus, have been reported with use of pancreatic enzyme products. Seek medical attention if signs or symptoms of a hypersensitivity reaction develop *[see Warnings and Precautions (5.5)]*.

Dosage

Advise the patient or caregiver to take ZENPEP as prescribed, and to contact the healthcare provider if signs and symptoms of malabsorption persist *[see Dosage and Administration (2.2)]*.

Administration

Instruct the patient or caregiver as follows:
- Take ZENPEP with meals or snacks.
- Swallow capsules whole.

- For adult and pediatric patients who are unable to swallow intact capsules, the capsule contents may be sprinkled on a small amount of acidic soft food with a pH of 4.5 or less (e.g., commercially available preparations of applesauce, bananas, or pears). For pediatric patients birth to 12 months of age, ZENPEP capsules can also be opened, and the capsule contents sprinkled directly into the infant's mouth.
- Consume sufficient liquids (juice, water, breast milk, or formula) and visually inspect an infant's mouth to ensure complete swallowing of ZENPEP capsules or capsule contents *[see Warnings and Precautions (5.2)]*.
- Do not crush or chew ZENPEP capsules or capsule contents.
- Do not mix the ZENPEP capsule contents directly into a bottle of breast milk or formula.

Storage

Instruct the patient or caregiver as follows:

- Keep ZENPEP in a dry place and protect from moisture and heat.
- After opening, keep bottle tightly closed between uses to protect from moisture.
- Keep the desiccant in the bottle, if present. The desiccant packet should not be eaten or thrown away.

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