## 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**
**Initial U.S. Approval: 2009**

### INDICATIONS AND USAGE

ZENPEP is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions (1)

### DOSAGE AND ADMINISTRATION

*Dosage*

ZENPEP is not interchangeable with any other pancrelipase product.

*Infants (up to 12 months)*

- Infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. (2.1)
- Do not mix ZENPEP capsule contents directly into formula or breast milk prior to administration. (2.2)

*Children Older than 12 Months and Younger than 4 Years*

- Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.1)

*Children 4 Years and Older and Adults*

- Enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day. (2.1)

*Limitations on Dosing*

- Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines (2.1)

*Administration*

- ZENPEP should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food, e.g., applesauce. (2.2)

### DOSAGE FORMS AND STRENGTHS

- Delayed-Release Capsules: 3,000 USP units of lipase; 10,000 USP units of protease; 14,000 USP units of amylase. Capsules have a white opaque cap and body, printed with "APTALIS 3" (3)
- Delayed-Release Capsules: 5,000 USP units of lipase; 17,000 USP units of protease; 24,000 USP units of amylase. Capsules have a white opaque cap and body, printed with "APTALIS 5" (3)
- Delayed-Release Capsules: 10,000 USP units of lipase; 32,000 USP units of protease; 42,000 USP units of amylase. Capsules have a yellow opaque cap and white opaque body, printed with "APTALIS 10" (3)
- Delayed-Release Capsules: 15,000 USP units of lipase; 47,000 USP units of protease; 63,000 USP units of amylase. Capsules have a red opaque cap and white opaque body, printed with "APTALIS 15" (3)
- Delayed-Release Capsules: 20,000 USP units of lipase; 63,000 USP units of protease; 84,000 USP units of amylase. Capsules have a green opaque cap and white opaque body, printed with "APTALIS 20" (3)
- Delayed-Release Capsules: 25,000 USP units of lipase; 79,000 USP units of protease; 105,000 USP units of amylase. Capsules have a blue opaque cap and white opaque body, printed with "APTALIS 25" (3)
- Delayed-Release Capsules: 40,000 USP units of lipase; 126,000 USP units of protease; 168,000 USP units of amylase. Capsules have an orange opaque cap and white opaque body, printed with "APTALIS 40" (3)
- Delayed-Release Capsules: 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 printed with two black stripes and white opaque body, printed with "APTALIS 60" (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- 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). (5.1)
- To avoid irritation of oral mucosa, do not chew ZENPEP or retain in the mouth. (5.2)
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia. (5.3)
- There is theoretical risk of viral transmission with all pancreatic enzyme products including ZENPEP. (5.4)
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin. (5.5)

### ADVERSE REACTIONS

- The most common adverse events (≥6% of patients treated with ZENPEP) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety, and contusion. (6.1)

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

### USE IN SPECIFIC POPULATIONS

**Pediatric Patients:**

- The safety and effectiveness of ZENPEP were assessed in pediatric patients, ages 1 to 17 years. (8.4)
- The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase in pediatric patients have been described in the medical literature and through clinical experience. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 10/2023**

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**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 due to cystic fibrosis or other conditions.

# 2 DOSAGE AND ADMINISTRATION

## 2.1 Dosage

ZENPEP is not interchangeable with other pancrelipase products.

ZENPEP is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of ZENPEP should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet (see Limitations on Dosing below).

ZENPEP is a mixture of enzymes including lipases, proteases, and amylases and dosing is based on lipase units. Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1, 2, 3] ZENPEP should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraphs, with one exception. The Conferences recommend doses of 2,000 to 4,000 lipase units in infants up to 12 months. ZENPEP is available in a 3,000 lipase unit capsule. The recommended dose of ZENPEP in infants up to 12 months is 3,000 lipase units. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme.

*Infants (up to 12 months)*

Infants may be given 3,000 lipase units (one capsule) per 120 mL of formula or breast-feeding. Do not mix ZENPEP capsule contents directly into formula or breast milk prior to administration *[see Dosage and Administration (2.2)]*.

*Children Older than 12 Months and Younger than 4 Years*

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

*Children 4 Years and Older and Adults*

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed ZENPEP dose for an individualized full meal should be given with each snack. The total daily dose should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

*Limitations on Dosing*

Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.[1, 2, 3]

If symptoms and signs of steatorrhea persist, the dosage may be increased by a healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted.

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. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures, indicative of fibrosing colonopathy, in children with cystic fibrosis less than 12 years of age *[see Warnings and Precautions (5.1)]*. Patients currently 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.

### 2.2 Administration

ZENPEP should always be taken as prescribed by a healthcare professional.

*Infants (up to 12 months)*

ZENPEP should be administered to infants immediately prior to each feeding, using a dosage of 3,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Contents of the capsule may be administered with a small amount of applesauce, or other acidic food with a pH of 4.5 or less (e.g., commercially available preparations of bananas, or pears). Contents of the capsule may also be administered directly to the mouth. Administration should be followed by breast milk or formula. Contents of the capsule **should not** be mixed directly into formula or breast milk as this may diminish efficacy. Care should be taken to ensure that ZENPEP is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

*Children and Adults*

ZENPEP should be taken during meals or snacks, with sufficient fluid. **ZENPEP capsules and capsule contents should not be crushed or chewed.** Capsules should be swallowed whole.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on small amounts of acidic soft food of pH 4.5 or less (e.g., commercially available preparations of bananas, pears and applesauce).

The ZENPEP -soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

## 3 DOSAGE FORMS AND STRENGTHS

Delayed-release capsules are available in the following:

- 3,000 USP units of lipase; 10,000 USP units of protease; 14,000 USP units of amylase. Capsules have a white opaque cap and white opaque body, red imprint with “APTALIS 3”
- 5,000 USP units of lipase; 17,000 USP units of protease; 24,000 USP units of amylase, Capsules have a white opaque cap and white opaque body, blue imprint with “APTALIS 5”
- 10,000 USP units of lipase; 32,000 USP units of protease; 42,000 USP units of amylase. Capsules have a yellow opaque cap and white opaque body, blue imprint with “APTALIS 10”
- 15,000 USP units of lipase; 47,000 USP units of protease; 63,000 USP units of amylase. Capsules have a red opaque cap and white opaque body, blue imprint with “APTALIS 15”
- 20,000 USP units of lipase; 63,000 USP units of protease; 84,000 USP units of amylase. Capsules have a green opaque cap and white opaque body, blue imprint with “APTALIS 20”
- 25,000 USP units of lipase; 79,000 USP units of protease; 105,000 USP units of amylase. Capsules have a blue opaque cap and white opaque body, blue imprint with “APTALIS 25”
- 40,000 USP units of lipase; 126,000 USP units of protease; 168,000 USP units of amylase. Capsules have an orange opaque cap and white opaque body, 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 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 6,000 lipase units/kg of body weight per meal have been associated with colonic strictures in children less than 12 years of age.[1] 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)]*.

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 of enzyme activity *[see Dosage and Administration (2.2) and Patient Counseling Information (17.1)]*. 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)]*.

### 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 5,000 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 have been identified during post-approval use of Zenpep. 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

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 estimated 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 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 years. The safety and efficacy in pediatric patients in this study were similar to adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

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)]*. 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)]*.

## 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)]*. 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)]*.

## 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.

ZENPEP (pancrelipase) delayed-release capsule for oral administration contains enteric-coated beads (1.8-1.9mm for 3,000 and 5,000 USP units of lipase, 2.2-2.5mm for 10,000, 15,000, 20,000, 25,000, 40,000 and 60,000 USP units of lipase) and available as follows:

**3,000 USP units of lipase**; 10,000 USP units of protease; 14,000 USP units of amylase. 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 imprinting blue ink on the capsules strengths 5,000, 10,000, 15,000, 20,000, 25,000 and 40,000 contains dehydrated alcohol, FD&C Blue #2 aluminum lake C.I. 73015-E132, isopropyl alcohol, n-butyl alcohol, propylene glycol, shellac and strong ammonia solution.

**5,000 USP units of lipase**; 17,000 USP units of protease; 24,000 USP units of amylase. 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.

**10,000 USP units of lipase**; 32,000 USP units of protease; 42,000 USP units of amylase. 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.

**15,000 USP units of lipase**; 47,000 USP units of protease; 63,000 USP units of amylase. 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.

**20,000 USP units of lipase**; 63,000 USP units of protease; 84,000 USP units of amylase. 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.

**25,000 USP units of lipase**; 79,000 USP units of protease; 105,000 USP units of amylase. 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.

**40,000 USP units of lipase**; 126,000 USP units of protease; 168,000 USP units of amylase. 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.

**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.

Inactive ingredients in ZENPEP include colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc, and triethyl citrate and are contained in hypromellose capsules. The imprinting red ink on the 3,000 capsules strength contains, antifoam DC 1510, industrial methylated spirit, iron oxide red C.I. 77491-E172, n-butyl alcohol, shellac and soya lecithin.

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

The pancreatic enzymes in ZENPEP 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.

## 12.3 Pharmacokinetics

The pancreatic enzymes in ZENPEP are enteric-coated to minimize destruction or inactivation in gastric acid. ZENPEP is designed to release most of the enzymes in vivo at pH greater than 5.5. Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

# 14 CLINICAL STUDIES

The short-term safety and efficacy of ZENPEP were evaluated in 2 studies conducted in 53 patients, ages 1 to 23 years, with exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF).

Study 1, was a randomized, double-blind, placebo-controlled, crossover study of 34 patients, ages 7 to 23 years, with EPI due to CF. 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 dose during the controlled treatment periods ranged from a mean dose of 3,900 lipase units per kilogram per day to 5,700 lipase units per kilogram per day. All patients consumed a high-fat diet (greater than or equal to 100 grams of fat per day) during the treatment period.

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 $p \leq 0.001$.

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 gender.

Study 2, was an open-label, uncontrolled study of 19 patients, ages 1 to 6 years (mean age 4 years), with EPI due to CF. Approximately half of the patients were ages 1 to 3 years. Study 2 compared a measurement of fat malabsorption, spot fecal fat testing, before (while receiving therapy with another commercial PEP) and after oral administration of Zenpep capsules with each meal or snack.

All patients in Study 2 were transitioned to ZENPEP from their usual PEP treatment. 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 5,000 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 wash-out period. Overall, patients showed similar control of fat malabsorption by spot fecal fat testing when switched to ZENPEP treatment at similar doses.

## 15 REFERENCES


1. Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *Journal of Pediatrics*. 1995; 127: 681-684.
2. Borowitz DS, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *Journal of Pediatric Gastroenterology Nutrition*. 2002 Sep; 35: 246-259.
3. Stallings VA, Start LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association*. 2008; 108: 832-839.
4. Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study.9 *Lancet*. 1995; 346: 1247-1251.
5. FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *New England Journal of Medicine*. 1997; 336: 1283-1289.


## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZENPEP® (pancrelipase) Delayed-Release Capsules

3,000 USP units of lipase; 10,000 USP units of protease; 14,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with white opaque cap and white body with a red radial print and printed with "APTALIS 3", *that contains* 1.8-1.9mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-113-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

5,000 USP units of lipase; 17,000 USP units of protease; 24,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with white opaque cap and white body with a blue radial print and printed with "APTALIS 5", *that contains* 1.8-1.9mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-115-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

10,000 USP units of lipase; 32,000 USP units of protease; 42,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with yellow opaque cap and white body with a blue radial print and printed with “APTALIS 10”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-110-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

15,000 USP units of lipase; 47,000 USP units of protease; 63,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with red opaque cap and white body with a blue radial print and printed with “APTALIS 15”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-111-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

20,000 USP units of lipase; 63,000 USP units of protease; 84,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with green opaque cap and white body with a blue radial print and printed with “APTALIS 20”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-112-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

25,000 USP units of lipase; 79,000 USP units of protease; 105,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with blue opaque cap and white body with a blue radial print and printed with “APTALIS 25”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-116-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

40,000 USP units of lipase; 126,000 USP units of protease; 168,000 USP units of amylase.

Each ZENPEP capsule is available as a two piece hypromellose capsule with orange opaque cap and white body with a blue radial print and printed with “APTALIS 40”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-114-01)

ZENPEP® (pancrelipase) Delayed-Release Capsules

60,000 USP units of lipase; 189,600 USP units of protease; 252,600 USP units of amylase.

Each ZENPEP capsule is available as a 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”, that contains 2.2-2.5mm enteric-coated beads. Capsules are supplied in bottles of:

- 100 capsules (NDC 73562-117-01)

**Storage and Handling**

Original container:

Avoid excessive heat. Store at room temperature, 20°C to 25°C (68°F to 77°F), and brief excursions permitted to 15°C to 40°C (59°F to 104°F) for 24 hours. Protect from moisture. AFTER OPENING, KEEP BOTTLE TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE.

Repackaged HDPE container:

Avoid excessive heat. Store at up to 30°C (86°F) for up to 6 months. 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.

Dispense in tight container (USP).

Keep out of reach of children.

DO NOT CRUSH ZENPEP delayed-release capsules.

# 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

## 17.1 Dosing and Administration

- Instruct patients and caregivers that ZENPEP should only be taken as directed by their healthcare professional. Patients should be advised that the total daily dose should not exceed 10,000 lipase units/kg body weight per day unless clinically indicated. This needs to be especially emphasized for patients eating multiple snacks and meals per day. Patients should be informed that if a dose is missed, the next dose should be taken with the next meal or snack as directed. Doses should not be doubled *[see Dosage and Administration (2)]*.
- Instruct patients and caregivers that ZENPEP should always be taken with food. Patients should be advised that ZENPEP delayed-release capsules must not be crushed or chewed as doing so could cause early release of enzymes and/or loss of enzymatic activity. Patients should swallow the intact capsules with adequate amounts of liquid at mealtimes. If necessary, the capsules contents can also be sprinkled on soft acidic foods *[see Dosage and Administration (2)]*.
- Instruct patients to notify their healthcare professional if they are pregnant or are thinking of becoming pregnant during treatment with ZENPEP *[see Use in Specific Populations (8.1)]*.
- Instruct patients and caregivers to notify the healthcare professional if the patient has a history of abnormal glucose levels before initiating treatment with ZENPEP *[see Postmarketing Experience (6.2)]*.

## 17.2 Fibrosing Colonopathy

Advise patients and caregivers to follow dosing instructions carefully, as doses of pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal (10,000 lipase units/kg body weight/day) have been associated with colonic strictures in children below the age of 12 years *[see Dosage and Administration (2)]*.

### 17.3 Allergic Reactions

Advise patients and caregivers to contact their healthcare professional immediately if allergic reactions to ZENPEP develop *[see Warnings and Precautions (5.5)]*.

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