HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PANCREAZE® safely and effectively. See full prescribing information for PANCREAZE®.

PANCREAZE® (pancrelipase) delayed-release capsules

Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------

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

----------DOSAGE AND ADMINISTRATION----------

Important Dosing Information (2.1)

- PANCREAZE 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 PANCREAZE. When switching from another pancreatic enzyme product to PANCREAZE, 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 and older.
- 1,000 lipase units/kg/meal for pediatric patients greater than 12 months to less than 4 years.
- Titrate the dosage to either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or less than 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 2,600 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).
- Do not crush or chew PANCREAZE capsules or capsule contents.
- Consume sufficient liquids to ensure complete swallowing of PANCREAZE. (5.2)
- See the full prescribing information for additional information on administering to pediatric patients birth to 12 months.

----------DOSAGE FORMS AND STRENGTHS----------

Delayed-release capsules (3):

- 2,600 USP units of lipase; 8,800 USP units of protease; and 15,200 USP units of amylase.
- 4,200 USP units of lipase; 14,200 USP units of protease; and 24,600 USP units of amylase
- 10,500 USP units of lipase; 35,500 USP units of protease; and 61,500 USP units of amylase
- 16,800 USP units of lipase; 56,800 USP units of protease; and 98,400 USP units of amylase
- 21,000 USP units of lipase; 54,700 USP units of protease; and 83,900 USP units of amylase
- 37,000 USP units of lipase; 97,300 USP units of protease; and 149,900 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, 5.3)
- 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 are gastrointestinal, including nausea and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact VIVUS LLC at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

PANCREAZE is a mixture of enzymes including lipases, proteases, and amylases. PANCREAZE 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 PANCREAZE dose for a meal.
- Do not substitute other pancreatic enzyme products for PANCREAZE. When switching from another pancreatic enzyme product to PANCREAZE, 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 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 and symptoms of malabsorption including measures of nutritional status.

Pediatric Patients Birth to 12 Months of Age
The recommended oral dosage is 2,600 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 PANCREAZE with 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., applesauce). Consume the entire mixture immediately.
- Do not crush or chew PANCREAZE capsules or capsule contents.
- Consume sufficient liquids (water or juice) to ensure complete swallowing of PANCREAZE capsules *[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 PANCREAZE capsule (containing 2,600 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., applesauce) 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 PANCREAZE to ensure complete swallowing of the capsule contents.
- Do not mix PANCREAZE capsule contents directly into a bottle of breast milk or formula.
- Do not crush PANCREAZE 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:

- 2,600 USP units of lipase; 8,800 USP units of protease; and 15,200 USP units of amylase in a two-piece hypromellose capsule with a light orange opaque body and clear cap, printed with "VIVUS" and "MT 2"

- 4,200 USP units of lipase; 14,200 USP units of protease; and 24,600 USP units of amylase in a two-piece hypromellose capsule with a yellow opaque body and clear cap, printed with "VIVUS" and "MT 4"
- 10,500 USP units of lipase; 35,500 USP units of protease; and 61,500 USP units of amylase in a two-piece hypromellose capsule with a flesh opaque body and clear cap, printed with "VIVUS" and "MT 10"
- 16,800 USP units of lipase; 56,800 USP units of protease; and 98,400 USP units of amylase in a two-piece hypromellose capsule with a flesh opaque body and clear cap, printed with "VIVUS" and "MT 16"
- 21,000 USP units of lipase; 54,700 USP units of protease; and 83,900 USP units of amylase in a two-piece hypromellose capsule with a white opaque body and cap, printed with "VIVUS" and "MT 20"
- 37,000 USP units of lipase; 97,300 USP units of protease; and 149,900 USP units of amylase in a two-piece hypromellose capsule with an iron grey opaque body and white opaque cap, printed with "VIVUS" and "MT 37"

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 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 strictures, 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 PANCREAZE 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 and 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 PANCREAZE 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., applesauce).
- Do not crush or chew PANCREAZE capsules or capsule contents.
- Consume sufficient liquids (juice, water, breast milk, or formula) immediately following administration of PANCREAZE 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 that 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 PANCREAZE.

5.4 Risk of Viral Transmission

PANCREAZE is sourced from pancreatic tissue from swine used for food consumption. Although the risk that PANCREAZE 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

Serious hypersensitivity reactions including anaphylaxis, asthma, hives, and pruritus have been reported with pancreatic enzyme products *[see Adverse Reactions (6)]*. 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 PANCREAZE. The risks and benefits of continued PANCREAZE treatment in patients with serious 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)]*

The data described below reflect exposure to PANCREAZE in 57 adult and pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis in two clinical trials. Study 1 was conducted in 40 patients, aged 8 years to 57 years; Study 2 was conducted in 17 pediatric patients, aged 6 months to 30 months *[see Clinical Studies (14)]*. The most common adverse reactions were gastrointestinal, including diarrhea and vomiting.

The following adverse reactions have been identified during post-approval use of PANCREAZE 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, distal intestinal obstruction syndrome
- abdominal pain, flatulence, constipation, and nausea

Immune System Disorders
- anaphylaxis, asthma, hives, and pruritus

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 PANCREAZE and any potential adverse effects on the breastfed infant from PANCREAZE or from the underlying maternal condition.

8.4 Pediatric Use

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

Use of PANCREAZE for this indication is supported by an adequate and well-controlled trial in adult and pediatric patients 8 to 17 years of age (Study 1) along with supportive data from a randomized, investigator-blinded, dose-ranging study in 17 pediatric patients aged 6 to 30 months (Study 2). Both study populations consisted of patients with exocrine pancreatic insufficiency due to cystic fibrosis. The safety in pediatric patients in these studies was similar to that observed in adult patients *[see Adverse Reactions (6) 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 PANCREAZE 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 PANCREAZE 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 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 PANCREAZE 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

In Study 1, a 10 year-old patient was administered a PANCREAZE dose of 12,399 lipase units/kg/day for the duration of the open-label and randomized withdrawal periods (21 days). The patient experienced mild abdominal pain throughout both study periods. Abnormal chemistry data at the end of the study included mild elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum phosphate. Abnormal hematology data at the end of the study included mild elevations of hematocrit. No abnormalities from analyses of urinalysis or uric acid were noted.

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 microtablets in PANCREAZE are formulated to release pancreatic enzymes at an approximate pH of 5.5 or greater.

PANCREAZE (pancrelipase) delayed-release capsules are for oral administration and include a two-piece shell containing enteric-coated microtablets that are each approximately 2 mm in diameter and are available as follows:

2,600 USP units of lipase**;** 8,800 USP units of protease; and 15,200 USP units of amylase; delayed-release capsules have a light orange opaque body and clear cap imprinted with "VIVUS" and "MT 2". The shells contain hypromellose, titanium dioxide, yellow iron oxide, red iron oxide and imprint ink contains black iron oxide, shellac, propylene glycol, strong ammonia solution, potassium hydroxide.

4,200 USP units of lipase; 14,200 USP units of protease; and 24,600 USP units of amylase; delayed-release capsules have a yellow opaque body and clear cap imprinted with "VIVUS" and

“MT 4”. The shells contain hypromellose, titanium dioxide, yellow iron oxide, and imprint ink contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

10,500 USP units of lipase; 35,500 USP units of protease; and 61,500 USP units of amylase; delayed-release capsules have a flesh opaque body and clear cap imprinted with “VIVUS” and “MT 10”. The shells contain hypromellose, titanium dioxide, red iron oxide, and imprint ink contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

16,800 USP units of lipase; 56,800 USP units of protease; 98,400 USP units of amylase; delayed-release capsules have a flesh opaque body and clear cap imprinted with “VIVUS” and “MT 16”. The shells contain hypromellose, titanium dioxide, red iron oxide, yellow iron oxide, and imprint ink contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

21,000 USP units of lipase; 54,700 USP units of protease; and 83,900 USP units of amylase; delayed-release capsules have a white opaque body and cap imprinted with “VIVUS” and “MT 20”. The shells contain hypromellose, titanium dioxide, and imprint ink contains yellow iron oxide, shellac, strong ammonia solution, propylene glycol.

37,000 USP units of lipase; 97,300 USP units of protease; and 149,900 USP units of amylase; delayed-release capsules have an iron grey opaque body and white opaque cap imprinted with “VIVUS” and “MT 37”. The shells contain hypromellose, titanium dioxide, black iron oxide and imprint ink contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

PANCREAZE (pancrelipase) delayed-release capsules include the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, methacrylic acid ethyl acrylate copolymer, microcrystalline cellulose, montan glycol wax, simethicone emulsion, 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 monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches 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 PANCREAZE 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 PANCREAZE are not absorbed from the gastrointestinal tract in appreciable amounts.

Drug Interactions

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

14 CLINICAL STUDIES

Studies 1 and 2 were conducted in 57 adult and pediatric patients, aged 6 months to 17 years, with exocrine pancreatic insufficiency due to cystic fibrosis.

Study 1

Study 1 was a randomized, double-blind, placebo-controlled study of 40 patients, ages 8 to 57 years. In this study, patients received PANCREAZE at individually titrated doses (not to exceed 2,500 lipase units/kg/meal) for 14 days (open-label period) followed by randomization to PANCREAZE or matching placebo for 7 days of treatment (double-blind withdrawal period). Only patients with coefficient of fat absorption (CFA) ≥80% in the open-label period were randomized to the double-blind withdrawal period. The mean dosage during the 70day placebo-controlled treatment period was 6,400 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 change in CFA from the open label period to the end of the double-blind withdrawal period. The CFA was determined by a 72-hour stool collection period during both treatment periods, when both fat excretion and fat ingestion were measured (Table 1).

Table 1. Change in CFA in Study 1 (Open-Label Period to End of Double-Blind Withdrawal Period)

	PANCREAZE N=20	Placebo N=20
CFA [%]		
Open-Label Period[a] (Mean, SD)	88 (5)	91 (5)
End of Double-Blind Withdrawal Period[b] (Mean, SD)	87 (8)	56 (25)
Change in CFA[c] [%]		
Open-Label Period to End of Double-Blind Withdrawal Period (Mean, SD)	-2 (6)	-34 (23)
Treatment Difference Point Estimate (95% CI)	33 (25, 40)	

[a] Minimum of 72 hours from start of open label period.
[b] Double-blind withdrawal period ranged from 4 to 7 days.
[c] $p<0.001$

At the end of the double-blind withdrawal period, the mean change in CFA from the open-label period to the end of the double-blind withdrawal period was -2% with PANCREAZE treatment compared to -34% with placebo treatment. There were similar responses to PANCREAZE by age and biological sex.

Study 2

Study 2 was a randomized, investigator-blinded, dose-ranging study of 17 pediatric patients, ages 6 months to 30 months (mean 18 months). The final analysis population was limited to 16 patients; 1 patient was excluded due to withdrawal of consent. All patients were transitioned from their usual pancreatic enzyme treatment to PANCREAZE at 375 lipase units/kg/meal for a 6-day run-in period. Patients were then randomized to receive PANCREAZE at one of four dosages (375, 750, 1,125, and 1,500 lipase units/kg/meal) for 5 days.

Coefficient of Fat Absorption Endpoint and Results

The CFA was measured at the end of the run-in period and at the end of the randomized period (Table 2).

Table 2. Change in CFA in Study 2 (End of Run-in Period to End of Study)

	375 lipase units /kg/meal N=4	750 lipase units /kg/meal N=4	1,125 lipase units /kg/meal N=4	1,500 lipase units /kg/meal N=4
CFA (%)				
Day 6[a] (Mean, SD)	93 (2)	90 (5)	81 (11)	93 (3)
Day 11[b] (Mean, SD)	92 (3)	91 (4)	80 (13)	91 (2)
Change in CFA (%) Day 6 to Day 11 (Mean, SD)	-2 (3)	1 (3)	-1 (3)	-2 (3)

[a] End of Run-in Period; [b] End of Study

Overall, patients showed similar CFA at the end of the run-in period (mean PANCREAZE dosage of 1,600 lipase units/kg/day) and at the end of the study across the four treatment arms.

16 HOW SUPPLIED/STORAGE AND HANDLING

PANCREAZE (pancrelipase) delayed-release capsules are supplied as follows:

Strength	Description	Supplied As NDC Number
2,600 USP units of lipase; 8,800 USP units of protease; 15,200 USP units of amylase	two-piece hypromellose capsule with a light orange opaque body and clear cap imprinted with "VIVUS" and "MT 2"	Bottles of 100 NDC 62541-401-10
4,200 USP units of lipase; 14,200 USP units of protease; 24,600 USP units of amylase	two-piece hypromellose capsule with a yellow opaque body and clear cap imprinted with "VIVUS" and "MT 4"	Bottles of 100 NDC 62541-402-10
10,500 USP units of lipase; 35,500 USP units of protease; 61,500 USP units of amylase	two-piece hypromellose capsule with a pink opaque body and clear cap imprinted with "VIVUS" and "MT 10"	Bottles of 100 NDC 62541-403-10
16,800 USP units of lipase; 56,800 USP units of protease; 98,400 USP units of amylase	two-piece hypromellose capsule with a flesh opaque body and clear cap imprinted with "VIVUS" and "MT 16"	Bottles of 100 NDC 62541-404-10
21,000 USP units of lipase; 54,700 USP units of protease; 83,900 USP units of amylase	two-piece hypromellose capsule with a white opaque body and cap imprinted with "VIVUS" and "MT 20"	Bottles of 100 NDC 62541-405-10
37,000 USP units of lipase; 97,300 USP units of protease; 149,900 USP units of amylase	Two-piece hypromellose capsule with an iron grey opaque body and white opaque cap imprinted with "VIVUS" and "MT 37" amylase	2 bottles of 50-(NDC 62541-406-50) inside a carton (NDC 62541-406-10)

Storage and Handling

Store PANCREAZE at room temperature between 15ºC and 25ºC (59°F to 77°F), excursion permitted up to 40ºC (104°F) for 24 hours.

After opening, keep bottle tightly closed between uses to protect from moisture.

All PANCREAZE bottles contain a desiccant canister.

Store and dispense PANCREAZE in the original container.

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 or administer PANCREAZE 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 to:

- Take PANCREAZE with meals or snacks.
- Swallow capsules whole.
- For adult and pediatric patients unable to swallow intact capsules, the capsule contents may be sprinkled on a small amount soft acidic food with a pH of 4.5 or less (e.g., applesauce). For pediatric patients birth to 12 months of age, PANCREAZE 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 PANCREAZE capsules or capsule contents *[see Warnings and Precautions (5.2)]*.
- Do not crush or chew PANCREAZE capsules or capsule contents.

- Do not mix the PANCREAZE capsule contents directly into a bottle of breast milk or formula.

Storage
Instruct the patient or caregiver as follows:

- Keep PANCREAZE in a dry place and protect from moisture and heat.
- After opening, keep bottle tightly closed between uses to protect from moisture.
- Keep PANCREAZE in the original container.
- Do not eat or throw away the desiccant canister in the bottle.

Product of Germany

Finished Product Manufactured at:
Nordmark Pharma GmbH
25436 Uetersen, Germany.

Manufactured by:
VIVUS LLC
900 E. Hamilton Ave., Suite 550
Campbell, CA 95008 USA

MEDICATION GUIDE
PANCREAZE® (pan-kre-aze)
(pancrelipase)
delayed-release capsules

What is the most important information I should know about PANCREAZE?

PANCREAZE may increase your chance of having a rare bowel disorder called fibrosing colonopathy especially if taken at a high dose for a long time in children with cystic fibrosis. This condition is serious and may require surgery. The risk of having this condition may be reduced by following the dosing instructions that your doctor gave you. **Call your doctor right away if you have any unusual or severe**:

- stomach area (abdominal) pain
- bloating
- trouble passing stool (constipation)
- nausea, vomiting, or diarrhea

Take PANCREAZE exactly as prescribed by your doctor. Do not take more PANCREAZE than directed by your doctor.

What is PANCREAZE?

PANCREAZE is a prescription medicine used to treat people who cannot digest food normally because their pancreas does not make enough enzymes.

PANCREAZE contains a mixture of digestive enzymes including lipases, proteases, and amylases from pig pancreas.

PANCREAZE is safe and effective in adults and children.

Before taking PANCREAZE, tell your doctor about all your medical conditions, including if you:

- are allergic to pork (pig) products.
- have a history of blockage of your intestines, or scarring or thickening of your bowel wall (fibrosing colonopathy).
- have gout, kidney disease, or high blood uric acid (hyperuricemia).
- have trouble swallowing capsules.
- have any other medical condition.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if PANCREAZE passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take PANCREAZE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take PANCREAZE?

- **Take PANCREAZE exactly as your doctor tells you.** Contact your doctor if you continue to have signs and symptoms of malabsorption (not absorbing nutrients from food) such as abdominal pain, bloating, fatty stools, or weight loss. Your dose may need to be changed.
- You should not switch PANCREAZE with any other pancreatic enzyme product without first talking to your doctor.
- Do not take more capsules in a day than the number your doctor tells you (total daily dose).
- **Always take PANCREAZE with a meal or snack** and enough liquid (water, juice breast milk, or formula) to swallow PANCREAZE completely. If you eat a lot of meals or snacks in a day, be careful not to go over your total daily dose.
- Your doctor may change your dose based on the amount of fatty foods you eat or based on your weight.
- **PANCREAZE capsules should be swallowed whole. Do not crush or chew PANCREAZE capsules or its contents, and do not hold the capsule contents in your mouth.** Crushing, chewing or holding the PANCREAZE capsules in your mouth may cause irritation in your mouth or change the way PANCREAZE works in your body.

Giving PANCREAZE to Infants (Children from Birth up to 12 Months of Age):

The two ways to give PANCREAZE to infants (children from birth to 12 months of age) are described below:

a) Giving with Acidic Soft Food

1. Before each breast-feeding session or each time you give 120 mL of formula, carefully open the capsule and sprinkle the entire contents of the capsule on a small amount of acidic food such as applesauce. These foods should be the kind found in baby food jars that you buy at the store, or other food recommended by your doctor.
2. Mix the capsule contents evenly through the food. Be careful not to crush the PANCREAZE capsule contents while mixing.
3. Give the PANCREAZE and food mixture to your infant right away. **Do not** store PANCREAZE that is mixed with food.
4. Give your infant enough formula or breastfeed your infant **right away** to completely swallow the PANCREAZE food mixture.
5. Look into your infant's mouth to make sure that all the medicine has been swallowed.
6. Throw away the empty PANCREAZE capsule.

b) Giving Directly Into Infant's Mouth Before Breast or Formula Feeding

1. Before each breast-feeding session or each time you give 120 mL of formula, carefully open the PANCREAZE capsule and sprinkle the capsule contents directly into the infant's mouth.
2. **Do not** mix the PANCREAZE capsule contents directly into a bottle of breast milk or formula.
3. Give your infant additional breast milk or formula **right after** PANCREAZE to completely swallow the PANCREAZE capsule contents.
4. Look into your infant's mouth to make sure that all the medicine has been swallowed.
5. Throw away the empty PANCREAZE capsule.

- If a dose is missed, give the next dose with the next feeding.

Giving PANCREAZE to Adults and Children Older than 12 Months of Age:

- Swallow PANCREAZE capsules whole and take them with enough liquid (water or juice) to swallow them **right away.**
- If you have trouble swallowing capsules follow these instructions for taking PANCREAZE with food:
  - Carefully open the capsules and sprinkle the entire contents on a small amount of acidic food such as applesauce. Ask your doctor about other foods you can mix with PANCREAZE.
  - If you sprinkle PANCREAZE on food, **swallow it right after** you mix it and drink plenty of water or juice to make sure the medicine is swallowed completely. Do not store PANCREAZE that is mixed with food.
  - If you forget to take PANCREAZE, call your doctor or wait until your next meal and take your usual number of capsules. Take your next dose at your usual time. **Do not make up for missed doses.**

What are the possible side effects of PANCREAZE?
PANCREAZE may cause serious side effects, including:

- See **"What is the most important information I should know about PANCREAZE?"**
- **Irritation of the inside of your mouth.** This can happen if PANCREAZE is not swallowed completely.
- **Increase in blood uric acid levels (hyperuricemia).** This may happen in people with gout, kidney problems, or those who take high doses of pancrelipase, the active ingredient in PANCREAZE. Call your doctor if you have pain, stiffness, redness or swelling in your joints.
- **Severe allergic reactions.** Severe allergic reactions have happened in people taking pancreatic enzyme products like PANCREAZE. Stop taking PANCREAZE and get emergency treatment right away if you have any of these symptoms: trouble with breathing, skin rashes, swollen lips, or itching.

The most common side effects of PANCREAZE include:

- stomach (abdominal area) problems including nausea and vomiting.

Other possible side effects of PANCREAZE:

PANCREAZE and other pancreatic enzyme products are made from the pancreas of pigs, the same pigs people eat as pork. These pigs may carry viruses. Although it has never been reported, it may be possible for a person to get a viral infection from taking pancreatic enzyme products that come from pigs.

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of PANCREAZE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to VIVUS LLC at 1-888-998-4887.

How should I store PANCREAZE?

- Store PANCREAZE at room temperature between 59°F and 77°F (15°C and 25°C). Avoid heat.
- Keep PANCREAZE in a dry place and in the original container.
- After opening the bottle, keep it tightly closed between uses.
- All PANCREAZE bottles contain a desiccant canister. **Do not** eat or throw away the desiccant canister in your medicine bottle. This canister will protect your medicine from moisture.

Keep PANCREAZE and all medicines out of the reach of children.

General information about PANCREAZE

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PANCREAZE for a condition for which it was not prescribed. Do not give PANCREAZE to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or doctor for information about PANCREAZE that is written for healthcare professionals.

What are the ingredients in PANCREAZE?

Active Ingredient: lipase, protease, amylase

Inactive ingredients in all strengths of PANCREAZE: colloidal silicon dioxide, crospovidone, magnesium stearate, methacrylic acid ethyl acrylate copolymer, microcrystalline cellulose, montan glycol wax, simethicone emulsion, talc and triethyl citrate. The capsule shell contains hypromellose, titanium dioxide and iron oxide.

Imprint ink for PANCREAZE 2600 contains black iron oxide, shellac, propylene glycol, strong ammonia solution, potassium hydroxide.

Imprint ink for PANCREAZE 4200, 10500 and 16800 contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

Imprint ink for PANCREAZE 21000 contains yellow iron oxide, shellac, strong ammonia solution, propylene glycol.

Imprint ink for PANCREAZE 37000 contains black iron oxide, shellac-glaze-45%, ammonium hydroxide, propylene glycol.

For more information go to www.pancreaze.net or call 1-888-998-4887.

VIVUS®

Product of Germany
Finished Product Manufactured at:
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Manufactured by:
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U.S. License No. 2197

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