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

PERTZYE (pancrelipase) delayed-release capsules, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dosage (2.1)	10/2016
Dosage and Administration, Administration (2.2)	10/2016

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

PERTZYE® 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

PERTZYE® is not substitutable with any other pancrelipase product. (2.1)

Infants (up to 12 months)

- Infants may be given 4,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. (2.1)
- Do not mix PERTZYE 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

- PERTZYE capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents. For infants or patients unable to swallow capsules, the contents may be mixed with soft acidic food with a pH of 4.5 or less, e.g., applesauce. (2.2)

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

- Delayed-Release Capsules: 4,000 USP units of lipase; 14,375 USP units of protease; 15,125 USP units of amylase. (3)
- Delayed-Release Capsules: 8,000 USP units of lipase; 28,750 USP units of protease; 30,250 USP units of amylase. (3)
- Delayed-Release Capsules: 16,000 USP units of lipase; 57,500 USP units of protease; 60,500 USP units of amylase. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of PERTZYE 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 PERTZYE or retain in the mouth. (5.2)
- Hyperuricemia may develop. Consider monitoring uric acid levels in patients with hyperuricemia, gout, or renal impairment. (5.3)
- There is theoretical risk of viral transmission with all pancreatic enzyme products including PERTZYE. (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 reactions (≥ 10% of patients treated with PERTZYE) are diarrhea, dyspepsia, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Digestive Care Inc. at 1-877-882-5950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- 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: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

PERTZYE is not substitutable with other pancrelipase products.

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

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.[1,2,3] PERTZYE should be administered in a manner consistent with the recommendations of the Conferences provided in the following paragraphs. 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 4,000 lipase units (one capsule) per 120 mL of formula or breast-feeding. Do not mix PERTZYE 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 PERTZYE 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

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

Infants (up to 12 months)
PERTZYE should be administered to infants immediately prior to each feeding, using a dosage of 4,000 lipase units (one capsule) per 120 mL of formula or per breast-feeding. Contents of the capsule may be mixed with soft acidic food with a pH of 4.5 or less (e.g., applesauce). 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 the PERTZYE microspheres are not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

Children and Adults
PERTZYE should be taken during meals or snacks, with sufficient fluid. PERTZYE capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents mixed with small amounts of acidic soft food with a pH of 4.5 or less (e.g., applesauce). The PERTZYE-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 to avoid mucosal irritation.

Any unused portion of capsule contents should be discarded, and not used for subsequent dosing. The remaining exposed contents may lose potency and become less effective.

3 DOSAGE FORMS AND STRENGTHS

The active ingredient in PERTZYE evaluated in clinical trials is lipase. PERTZYE is dosed by lipase units.

PERTZYE is available in 3 color coded capsule strengths. Each PERTZYE delayed-release capsule strength contains the specified amounts of lipase, protease and amylase as follows:

- 4,000 USP units of lipase; 14,375 USP units of protease; 15,125 USP units of amylase. Delayed-release capsules have a clear body printed in green with "4" and a clear cap printed with a green circular stripe and "DCI"

- 8,000 USP units of lipase; 28,750 USP units of protease; 30,250 USP units of amylase. Delayed-release capsules have a clear body printed in blue with "8" and a clear cap printed with a blue circular stripe and "DCI"

- 16,000 USP units of lipase; 57,500 USP units of protease; 60,500 USP units of amylase. Delayed-release capsules have a clear body printed in red with "16" and a clear cap printed with a red circular stripe and "DCI"

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products.[4,5] 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.[1] 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. PERTZYE 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 mixed with a small amount of acidic soft food with a pH of 4.5 or less, such as applesauce. The PERTZYE-soft food mixture should be swallowed immediately and followed with water or juice to ensure complete ingestion.

5.3 Potential for Risk of Hyperuricemia

Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels. Consider monitoring serum uric acid levels in patients with hyperuricemia, gout, or renal impairment.

5.4 Potential Viral Exposure from the Product Source

PERTZYE is sourced from pancreatic tissue from swine used for food consumption. Although the risk that PERTZYE 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 PERTZYE 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 (5.1, 5.3, 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 short-term safety of PERTZYE was assessed in a randomized, double-blind, placebo-controlled, crossover study of 24 patients, ages 8 to 43 years, with exocrine pancreatic insufficiency due to cystic fibrosis. In this study, patients were randomized to receive

PERTZYE at individually titrated doses (not to exceed 2,500 lipase units per kilogram per meal) or matching placebo for 6 to 8 days of treatment, followed by crossover to the alternate treatment for an additional 6 to 8 days. The length of exposure to PERTZYE during this study was 20-28 days, including the treatment period of 6 to 8 days, and the open label titration and transition periods of 7 to 10 days.

The most common adverse reactions (≥10%) were diarrhea, dyspepsia, and cough. Table 1 enumerates adverse reactions that occurred in at least 2 patients (greater than or equal to 10%) treated with PERTZYE at a higher rate than with placebo.

Table 1. Adverse Reactions Occurring in at Least 2 Patients (≥ 10%)

Adverse Reaction	PERTZYE n=21 n (%)	PLACEBO n=24 n (%)
Diarrhea	2 (10%)	1 (4%)
Dyspepsia	2 (10%)	1 (4%)
Cough	2 (10%)	1 (4%)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PERTZYE. 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.

This formulation of PERTZYE has been marketed since 2004 under the trademark PANCRECARB®. Two product complaints relating to an adverse drug reaction were reported. A mild allergic reaction (itching and red, blotchy rash on face) was reported by a patient with a known history of allergy to another pancrelipase product, and a dull headache was reported by another patient taking concomitant ursodeoxycholic acid. Both events resolved without sequelae after discontinuation of treatment.

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

The short-term safety and efficacy of PERTZYE were assessed in a randomized, double-blind, placebo-controlled, crossover study of 24 patients with exocrine pancreatic insufficiency due to cystic fibrosis, including 10 patients between 8 and 17 years of age. The safety and efficacy in 8 to 17 year old patients in this study were similar to adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

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 pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis have 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)]*. 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)]*.

10 OVERDOSAGE

In a clinical study, a 10 year-old patient was administered lipase doses over the maximum lipase dose of 2500 lipase units/kg/meal (Dose Stabilization 2799 lipase units/kg/meal; Wash-out/Re-Stabilization 2783 lipase units/kg/meal; and PERTZYE 2720 lipase units/kg/meal). Despite the administration of this slightly (10%) higher than recommended dose, no gastrointestinal AEs were reported for this subject.

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

PERTZYE is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands. Pancrelipase contains multiple enzyme classes, including porcine-derived lipases, proteases, and amylases.

Pancrelipase is a beige-white amorphous powder. It is miscible in water and practically insoluble or insoluble in alcohol and ether.

Each PERTZYE delayed-release capsule for oral administration contains bicarbonate-buffered enteric-coated microspheres ranging in size from 0.8 – 1.4 mm in diameter for 4,000 USP units of lipase and 0.8 – 2.2 mm in diameter for 8,000 and 16,000 USP units of lipase.

The active ingredient evaluated in clinical trials is lipase. PERTZYE is dosed by lipase units. Other active ingredients include protease and amylase.

Inactive ingredients in PERTZYE include sodium bicarbonate, sodium carbonate, cellulose acetate phthalate, sodium starch glycolate, diethyl phthalate, ursodiol, polyvinylpyrrolidone, and talc and are contained in hard gelatin capsules.

<u>4,000 USP units of lipase</u>; 14,375 USP units of protease; 15,125 USP units of amylase. Delayed-Release Capsules have a clear body printed in green with “4” and a clear cap printed with a green circular stripe and “DCI”. The imprinting ink on the capsule contains FD&C Blue #1, D&C Yellow #10, black iron oxide, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, shellac and ammonium hydroxide.

<u>8,000 USP units of lipase</u>; 28,750 USP units of protease; 30,250 USP units of amylase. Delayed-Release Capsules have a clear body printed in blue with “8” and a clear cap printed with a blue circular stripe and “DCI”. The imprinting ink on the capsule contains FD&C Blue #1, ethanol, methanol, n-butyl alcohol, propylene glycol, shellac and ammonium hydroxide.

<u>16,000 USP units of lipase</u>; 57,500 USP units of protease; 60,500 USP units of amylase. Delayed-Release Capsules have a clear body printed in red with “16” and a clear cap printed with a red circular stripe and “DCI”. The imprinting ink on the capsule contains FD&C Red #40, povidone, titanium dioxide, dehydrated alcohol, sodium hydroxide, butyl alcohol, propylene glycol, isopropyl alcohol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pancreatic enzymes in PERTZYE 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 maltotriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

The short-term safety and efficacy of PERTZYE were evaluated in a randomized, double-blind, placebo-controlled, crossover study conducted in 24 patients ages 8 to 43 years (mean age = 20 years) with exocrine pancreatic insufficiency due to cystic fibrosis.[6] The efficacy analysis population included 21 patients who completed both double-blind treatment periods. Patients were randomized to receive PERTZYE at individually titrated doses (not to exceed 2,500 lipase units per kilogram per meal) or matching placebo for 6 to 8 days of treatment, followed by crossover to the alternate treatment for an additional 6 to 8 days.

The primary efficacy endpoint was the mean difference in coefficient of fat absorption (CFA) between PERTZYE and placebo treatment. The CFA was determined by a 72- hour stool collection during both treatments, when both fat ingestion and excretion were measured.

Mean CFA was 83% with PERTZYE treatment compared to 46% with placebo treatment. The mean difference in CFA was 36 percentage points in favor of PERTZYE treatment with 95% CI: (28, 45) and $p<0.001$.

The coefficient of nitrogen absorption (CNA) was determined by a 72-hour stool collection during both treatments, when nitrogen excretion was measured and nitrogen ingestion from a controlled diet was estimated (based on the assumption that proteins contain 16% nitrogen). Each patient's CNA during placebo treatment was used as their no-treatment CNA value. Mean CNA was 79% with PERTZYE treatment compared to 47% with placebo treatment. The mean difference in CNA was 32 percentage points in favor of PERTZYE treatment and this was a statistically significant change.

There were no differences between children and adults in the severity of pancreatic insufficiency (placebo response) or in the magnitude of the response to PERTZYE.

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.
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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.
6. Konstan MW, et al. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Cross-Over Study to Evaluate the Effectiveness and Safety of a Novel Pancrelipase (PANCRECARB® MS-16) in Reducing Steatorrhea in Children and Adults with Cystic Fibrosis. 2008 North American Cystic Fibrosis Conference. Abstract #618.

16 HOW SUPPLIED/STORAGE AND HANDLING

PERTZYE (pancrelipase) Delayed-Release Capsules
4,000 USP units of lipase; 14,375 USP units of protease; 15,125 units of amylase.
Each PERTZYE delayed-release capsule has a clear body printed in green with "4" and a clear cap printed with a green circular stripe and "DCI". Capsules are supplied in bottles of 100 (NDC 59767-004-01).

PERTZYE (pancrelipase) Delayed-Release Capsules
8,000 USP units of lipase; 28,750 USP units of protease; 30,250 units of amylase.
Each PERTZYE delayed-release capsule has a clear body printed in blue with "8" and a clear cap printed with a blue circular stripe and "DCI". Capsules are supplied in bottles of 100 (NDC 59767-008-01) or 250 (NDC 59767-008-02).

PERTZYE (pancrelipase) Delayed-Release Capsules
16,000 USP units of lipase; 57,500 USP units of protease; 60,500 units of amylase.
Each PERTZYE delayed-release capsule has a clear body printed in red with "16" and a clear cap printed with a red circular stripe and "DCI". Capsules are supplied in bottles of 100 (NDC 59767-016-01) or 250 (NDC 59767-016-02).

Storage and Handling

Store at room temperature 20- 25°C (68-77°F), brief excursions permitted to 15-40°C (59-104°F). PERTZYE hard gelatin capsules should be stored in a dry place in the original container. After opening, keep the container tightly closed between uses to protect from moisture.

PERTZYE is dispensed in bottles containing a desiccant. The desiccant packet should not be eaten or thrown away. The desiccant packet will protect the product from moisture.

Do not crush PERTZYE delayed-release capsules or the capsule contents.

17 PATIENT COUNSELING INFORMATION

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

17.1 Dosing and Administration

- Instruct patients and caregivers that PERTZYE 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/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 PERTZYE should always be taken with food. Patients should be advised that PERTZYE delayed-release capsules and the capsule contents must not be crushed or chewed as doing so could cause early release of enzymes and/or loss of enzymatic activity and irritation to the oral mucosa. Patients should swallow the intact capsules with adequate amounts of liquid at mealtimes. If necessary, the capsule contents can also be mixed with soft acidic foods. *[see Dosage and Administration (2)]*
- Any unused portion of capsule contents should be discarded, and not used for subsequent dosing. The remaining exposed contents may lose potency and become less effective. *[see Dosage and Administration (2)]*
- Instruct patients to keep out of the reach of children.

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) and Warnings and Precautions (5.1)]*

17.3 Allergic Reactions

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

17.4 Pregnancy and Breast Feeding

- Instruct patients to notify their physician if they are pregnant or are thinking of becoming pregnant during treatment with PERTZYE. *[see Use in Specific Populations (8.1)]*
- Instruct patients to notify their physician if they are breast feeding or are thinking of breast feeding during treatment with PERTZYE. *[see Use in Specific Populations (8.3)]*

Manufactured in the USA by:
Digestive Care, Inc.
Bethlehem, PA 18017

PERTZYE® is a registered trademark of Digestive Care, Inc.
U.S. Patent Numbers: 5,260,074; 5,302,400; 5,324,514; 5,460,812; 5,578,304; 5,750,104

MEDICATION GUIDE
PERTZYE (pert-zye)
(pancrelipase)
delayed-release capsules, for oral use

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

PERTZYE may increase your chance of having a rare bowel disorder called fibrosing colonopathy. This condition is serious and may require surgery. The risk of having fibrosing colonopathy 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
- diarrhea

Take PERTZYE exactly as prescribed by your doctor. **Do not** take more or less PERTZYE than your doctor tells you to.

What is PERTZYE?

- PERTZYE is a prescription medicine used to treat people who cannot digest food normally because their pancreas does not make enough enzymes due to cystic fibrosis or other conditions.
- PERTZYE capsules contain a mixture of digestive enzymes including lipases, proteases and amylases from pig pancreas.
- PERTZYE is safe and effective in children when taken as prescribed by your doctor.

Before taking PERTZYE, tell your doctor about all of 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.
- are pregnant or plan to become pregnant. It is not known if PERTZYE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if PERTZYE passes into your breast milk. You and your doctor should decide if you will take PERTZYE or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and 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 PERTZYE?

- **Take PERTZYE capsules exactly as your doctor tells you.**
- You should not switch PERTZYE with any other pancreatic enzyme product without first talking with your doctor.
- **Do not** take more capsules in a day than the number your doctor tells you to take (total daily dose).
- **Always take PERTZYE with a meal or snack and plenty of fluid**. 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.

PERTZYE capsules should be swallowed whole. Do not crush or chew the PERTZYE capsules or their contents, and do not hold the capsule or capsule contents in your mouth. Crushing, chewing or holding the PERTZYE capsules in your mouth may cause irritation in your mouth or change the way PERTZYE works in your body.

Giving PERTZYE to children and adults:

1. You should not divide the capsule contents into small amounts to give small doses of PERTZYE.
2. **Swallow PERTZYE capsules whole** and take them with enough liquid to swallow them right away.
3. If you have trouble swallowing capsules, open the capsules and mix the contents with a small amount of soft acidic food such as applesauce. Ask your doctor about other foods you can mix with PERTZYE.
4. If you mix PERTZYE with 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 PERTZYE that is mixed with food. Throw away any unused portion of the capsule contents.
5. If you forget to take PERTZYE, wait until your next meal or snack and take your usual number of capsules. Take your next dose at your usual time. **Do not take two doses at one time.**

What are the possible side effects of PERTZYE?

PERTZYE may cause serious side effects, including:

- See "**What is the most important information I should know about PERTZYE?**"
- **Irritation of the inside of your mouth**. This can happen if PERTZYE is not swallowed completely.
- **Increase in blood uric acid levels**. This may cause worsening of swollen, painful joints (gout) caused by an increase in your blood uric acid levels.
- **Allergic reactions, including trouble breathing, skin rash, itching, or swollen lips**.

Call your doctor right away if you have any of these symptoms.

The most common side effects of PERTZYE include:

- diarrhea
- upset stomach (indigestion)
- cough

Other possible side effects:

PERTZYE 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.

These are not all of the possible side effects of PERTZYE. 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 Digestive Care, Inc. at 1-877-882-5950.

How do I store PERTZYE?

- Store PERTZYE at room temperature between 68ºF to 77ºF (20°C to 25°C).
- Keep PERTZYE in a dry place and in the original container.
- After opening the bottle, keep it tightly closed between uses to keep your medicine dry (protect it from moisture).
- The PERTZYE bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). **Do not eat or throw away the packet (desiccant) in your medicine bottle**.

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

General information about the safe and effective use of PERTZYE.

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

You can ask your pharmacist or doctor for information about PERTZYE that is written for health professionals.

What are the ingredients in PERTZYE?

Active ingredients: lipase, protease, and amylase.

Inactive ingredients: sodium bicarbonate, sodium carbonate, cellulose acetate phthalate, sodium starch glycolate, diethyl phthalate, ursodiol, polyvinylpyrrolidone, and talc.

The hard gelatin capsule shells contain: gelatin and water.

The green imprinting ink on the 4,000 units of lipase; 14,375 units of protease; 15,125 units of amylase capsules contain: FD&C Blue #1, D&C Yellow #10, black iron oxide, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, shellac and ammonium hydroxide.

The blue imprinting ink on the 8,000 units of lipase; 28,750 units of protease; 30,250 units of amylase capsules contain: FD&C Blue #1, ethanol, methanol, n-butyl alcohol, propylene glycol, shellac and ammonium hydroxide.

The red imprinting ink on the 16,000 units of lipase; 57,500 units of protease; 60,500 units of amylase capsules contain: FD&C Red #40, povidone, titanium dioxide, dehydrated alcohol, sodium hydroxide, butyl alcohol, propylene glycol, isopropyl alcohol, and shellac.

Manufactured in the USA by: Digestive Care, Inc. Bethlehem, PA 18017

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For more information, go to www.digestivecare.com or call 1-877-882-5950.

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