SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PERTZYE® (pancrelipase) Delayed-Release Capsules, 8,000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains pancrelipase produced from porcine pancreatic tissue, equivalent to 8,000 units of lipase, 28,750 units of protease, and 30,250 units of amylase.

3 PHARMACEUTICAL FORM

Size 2, hard gelatin capsule, with a clear body printed in blue with "8" and a clear cap printed with a blue circular stripe and "DCI", containing enteric-coated microspheres.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

4.2 Posology and method of administration

Posology

PERTZYE is not substitutable with any other pancrelipase products.

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. 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. 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.

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.

Method of administration

Children and Adults
- Administer PERTZYE during meals or snacks, with sufficient fluid.
- Swallow PERTZYE capsules whole.
- If a dose is missed, take the next dose with the next meal or snack as directed. Do not take two doses at one time.
- Do not crush or chew the capsules or the capsule contents.
- For patients who are unable to swallow intact capsules, follow the instructions below for oral administration with soft foods with a pH of 4.5 or less (e.g., applesauce):
    1. Place a small amount (approximately 10 mL) of applesauce into a clean container.
    2. Carefully open the capsule(s).
    3. Sprinkle the intact microspheres on the applesauce.
    4. Mix the microspheres with the applesauce being careful not to crush the microspheres when mixing.
    5. Consume the entire contents immediately. Do not chew the microspheres. Do not save the applesauce and microspheres for later use.
    6. Follow with water or juice to ensure complete ingestion and to ensure nothing is retained in the mouth to avoid mucosal irritation.

4.3 Contraindications

Hypersensitivity to pancrelipase of porcine origin or to any of the excipients.

4.4 Special warnings and precautions for use

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. 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 section 4.2).

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 or enzyme activity.

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 (see section 4.2).

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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

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.

Breastfeeding

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.

Fertility

No fertility studies have been performed in animals.

4.7 Effects on ability to drive and use machines

PERTZYE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

A. Summary of the safety profile

The most common adverse reactions during treatment with PERTZYE include diarrhea, dyspepsia, and cough.

B. Tabulated list of adverse reactions

The following table displays adverse reactions that have been reported with the use of PERTZYE during clinical trials and post approval.

System Organ Class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)
Gastrointestinal Disorders	Diarrhea, dyspepsia	
Respiratory, Thoracic, and Mediastinal Disorder	Cough	
Nervous System Disorders		Headache*
Skin and Subcutaneous Tissue Disorders		Rash*

*See Section C.

C. Description of selected adverse reactions

Allergic reactions and headache have been reported as adverse reactions during post approval use. A patient reported a dull headache during concomitant use of ursodeoxycholic acid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions by contacting Digestive Care, Inc. at 1-877-882-5950.

4.9 Overdose

Chronic high doses of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures. 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 section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme preparations, ATC Code: A09AA02.

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.

Clinical efficacy and safety

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. 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, $p<0.001$.

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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate
Sodium carbonate
Cellulose acetate phthalate
Sodium starch glycolate
Diethyl phthalate
Ursodiol
Polyvinylpyrrolidone
Talc

<u>Capsule composition</u>
Water
Gelatin

<u>Ink composition</u>
FD&C Blue #1
Ethanol
Methanol

n-Butyl alcohol
Propylene glycol
Shellac
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 Months.

6.4 Special precautions for storage

Store at room temperature 20-25^{o}C (68-77^{o}F), brief excursions permitted to 15-40^{o}C (59-104^{o}F). PERTZYE should be stored in a dry place in the original container. After opening, keep 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.

6.5 Nature and contents of container

High density polyethylene bottles with child-resistant closures, containing 100 or 250 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Digestive Care, Inc.
1120 Win Drive
Bethlehem, PA 18017
1-877-882-5950

8 MARKETING AUTHORISATION NUMBER

US FDA NDA22175

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2012
Date of last renewal: 13 July 2017

10 DATE OF REVISION OF THE TEXT

12/2017