Medical Officer Labeling Review
Division of Gastroenterology and Inborn Error Products

NDA#: 22175/S-003
Sponsor: Digestive Care
Drug: Pertzye
Drug Classes: Pancreatic Enzyme Product (PEP)
Dose and Form: 4,000 lipase units / oral
Proposed Indication: The treatment of exocrine pancreatic insufficiency (b) (4) to cystic fibrosis and other conditions
Date Review Completed: September 19, 2016
Clinical Reviewer: Marjorie F. Dannis, M.D.
Team Leader: Anil Rajpal, M.D.

Background:
In 2012, Pertzye was originally approved for the treatment of exocrine pancreatic insufficiency (b) (4) to cystic fibrosis and other conditions. On 10/30/14, the CMC supplement which responded to PREA PMR 1894-1 for the development of an age appropriate formulation of Pertzye (listed below), received a complete response due to process validation deficiencies. On 6/10/16, Digestive Care submitted their response to CR for NDA 22175/S-003 Pertzye.

PMR 1894-1: Deferred requirement for development of an age appropriate formulation for Pertzye (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding

On September 21, 2016, PeRC was convened and concurred with DGIEP that the development of a 4,000 lipase unit capsule satisfied PREA PMR #1894-1 and thus it would be considered fulfilled.

From a clinical standpoint, below in *red italics*, are the proposed changes to the label (not yet negotiated with the Sponsor). These clinical changes pertain to the addition of the new dosage strength. Of note, although the Cystic Fibrosis Foundation Consensus Conferences Guidelines recommend that infants may be given 2,000-4,000 lipase units per 120 ml of formula or breast milk, for Pertzye, infants can be given 4,000 lipase units per 120 ml of formula or breast milk. [1] Thus, the appropriate adjustments have been made to the label.

[1] This has been an acceptable standard in the past for DGIEP (e.g Ultresa)

Labeling - Package Insert

A. Highlights of Prescribing Information:
INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION and DOSAGE FORMS AND STRENGTHS

----------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)

(b) (4)

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

Dosage

PERTZYE® is not (b) (4) with any other pancrelipase product.

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)*

----------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)

B. Full Prescribing Information (Dosage Section 2.1)

PERTZYE is not (b) (4) 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 and Weight 8 kg or Greater

(b) (4)

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 (b) (4) *nd Adults*

(b) (4)

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.

(b) (4)

C. Full Prescribing Information (Administration Section 2.2)

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.

D. Full Prescribing Information (Pediatric Use Section 8.4)

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.

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/s/

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09/22/2016

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09/22/2016