CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
Porcine-Derived Pancreatic Enzyme Products

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III

NDA:	22-175
Products:	Pancrecarb (pancrelipase) Delayed-Release Capsules
SPONSOR:	Digestive Care, Inc
FROM:	Julie Beitz, MD
DATE:	March 10, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Pancrecarb (pancrelipase) Delayed-Release Capsules to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with high doses of pancreatic enzyme products (PEPs), and the theoretical risk of transmission of viral disease to patients.

In reaching this determination, we considered the following:

A. The estimated size of the population likely to use the drug involved:

The estimated number of patients in the United States with maldigestion due to exocrine pancreatic insufficiency (EPI) is over 200,000.[1,2] This figure is based on estimates of the

[1] Cystic Fibrosis Foundation Patient Registry 2006. Annual Data Report to the Center Directors, Bethesda, MD. www.cff.org
[2] Russo MW, Wei JT, Thiny MT, et al. Digestive and liver disease statistics, 2004. *Gastroenterology* 2004;126:1448–1453.

number of patients with cystic fibrosis (30,000), various forms of pancreatitis (over 200,000), and other disorders such as pancreatectomy, all of which feature EPI.

B. The seriousness of the disease or condition that is to be treated with the drug:

Exocrine pancreatic insufficiency in patients with cystic fibrosis is associated with fat malabsorption and macro- and micronutrient malabsorption, and can lead to serious clinical conditions that include growth failure and impaired pulmonary function, which contribute to premature death. EPI due to, for example, chronic pancreatitis or pancreatectomy, is also associated with fat malabsorption and macro- and micronutrient malabsorption. These deficiencies can lead to serious clinical conditions that include wasting, vitamin K deficiency and coagulation abnormalities.

C. The expected benefit of the drug with respect to such disease or condition:

Patients with EPI due to cystic fibrosis will have improved growth, pulmonary function, and long-term survival. It is also standard medical practice to treat patients with EPI due to chronic pancreatitis, pancreatectomy, and other disorders because it is considered that PEP replacement will lead to clinical benefits including improved nutrition and decreased co-morbidities.

D. The expected or actual duration of treatment with the drug:

The expected duration of treatment with PEPs in patients with EPI is for the life of the patient.

E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug:

PEPs have been reported to cause fibrosing colonopathy, a serious condition that may lead to colonic stricture. Doses greater than 6,000 lipase units/kg of body weight (kg)/per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age. [3,4] The background incidence of such events is unknown. The Cystic Fibrosis Foundation (in conjunction with FDA) has established dosing guidelines that recommend that dosing not exceed 2,500 lipase units/kg of body weight (kg)/meal (or 10,000 lipase units/kg/day), or 4,000 lipase units/grams of fat ingested per day. Doses greater than 2,500 lipase units/kg/meal (or greater than 10,000 lipase units/kg/day) should only be used with caution and only if they are documented by laboratory testing that demonstrates improved fat absorption. Patients currently receiving higher doses than 6,000 lipase units/kg/meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

[3] Borowitz DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995; 127: 681-684.
[4] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, et. al. High-Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis. *N Eng J Med* 1997; 336:1283-9.

In addition to the known risk of fibrosing colonopathy, there is a theoretical risk for transmission of viral disease associated with treatment with porcine-derived PEPs. However, the risk of transmission of viruses that may be pathogenic to humans has not yet been determined, as no case of viral transmission in human has been documented.

F. Whether the drug is a new molecular entity (NME):

Pancrecarb (pancrelipase) Delayed-Release Capsules is a new chemical entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that porcine-derived PEPs, of which Pancrecarb (pancrelipase) Delayed-Release Capsules is a member of the class, pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of porcine-derived PEPs. FDA has determined that porcine-derived PEPs are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use porcine-derived PEPs. FDA has determined that porcine-derived PEPs are products that are important to health and patient adherence to directions for use is crucial to the drugs' effectiveness. FDA has also determined that porcine-derived PEPs are products for which patient labeling could help prevent serious adverse events.

The elements of the REMS for porcine-derived PEPs will be a Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

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