

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022523Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 12, 2010
FROM: Julie Beitz, MD
SUBJECT: Office Director Memo
TO: NDA 022523 Pancreaze (pancrelipase) Delayed-Release Capsules
Ortho-McNeil-Jansenn Pharmaceuticals, Inc.

Summary

Pancreaze (pancrelipase) Delayed-Release Capsules are an exogenous source of porcine-derived pancreatic enzymes. Pancreatic enzyme products (PEPs) serve as replacement therapy for digestive enzymes physiologically secreted by the pancreas and have long been considered the main stay of therapy for exocrine pancreatic insufficiency (EPI). Several PEPs, including Pancreaze, have been marketed in the US for many years and have not undergone review under new drug applications (NDAs). In 2004, to address concerns about variability in potency across products and within product lines, FDA published a Federal Register Notice which stated that PEPs must be marketed under approved NDAs.

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for the approval of Pancreaze (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. Discussions regarding product labeling, REMS, and postmarketing requirements and commitments, have concluded satisfactorily. There are no inspectional issues that would preclude approval of the application at this time.

Dosing

Pancreaze (pancrelipase) Delayed-Release Capsules are dosed by lipase units. As with other PEPs, the dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Pancreaze should be administered with meals in a manner consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Conferences. Product labeling will specify dosing recommendations for infants up to 12 months of age, for children 1-4 years of age, and for patients 4 years of age and older. Doses greater than 2500 lipase units/kg of body weight per meal (or 10,000 lipase units/kg of body weight per day) should be used with caution to minimize the risk of colonic stricture, indicative of fibrosing colonopathy.

Pancreaze (pancrelipase) Delayed-Release Capsules is not comparable to, or interchangeable with, other PEPs. The active pharmaceutical ingredient for all PEPs, including Pancreaze, is pancrelipase, which consists of the enzymes lipase, amylase and protease, as specified in the U.S. Pharmacopeia. However, the animal source of pancreata and the extraction processing differ among products. Thus, the **Dosage and Administration** section of the Pancreaze labeling will state that "Pancreaze is not interchangeable with any other pancrelipase product."

Regulatory History

On June 23, 2009, the applicant submitted NDA 022523 and was granted a standard review. A meeting of FDA's Anti-Viral Advisory Committee on December 2, 2008, focused on the theoretical risk of transmission of viral disease to patients exposed to porcine-derived PEPs, including Pancreaze (pancrelipase) Delayed-Release Capsules.

Efficacy

As with other PEP manufacturers, the applicant was requested to perform at least one controlled clinical trial with Pancreaze to demonstrate short-term efficacy and safety in the intended patient population in accordance with FDA's April 2006 *Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*.¹ The applicant conducted two clinical trials. One was a randomized, double-blind, placebo-controlled trial in 40 patients, aged 8-57 years (including 14 patients under 18 years of age), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients first received Pancreaze at individually titrated doses for 14 days (open label period), followed by randomization to either Pancreaze or matching placebo for 7 days (double-blind withdrawal period). The mean Pancreaze dose during the controlled treatment period was 6400 lipase units/kg of body weight per day. All patients consumed a high fat diet.

At the end of the double-blind withdrawal period, the mean change in the coefficient of fat absorption (CFA) in 72-hour stool samples from the open label period to the end of the double-blind withdrawal period was -1% on Pancreaze treatment compared with -34% on placebo treatment (p<0.001). There were similar responses to Pancreaze by age and gender.

The second was a randomized, investigator-blinded, dose-ranging trial in 17 pediatric patients aged 6 to 30 months (mean age 18 months) with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were transitioned from their usual PEP treatment to Pancreaze at 375 lipase units/kg of body weight per meal for 6 days (run-in period). Patients were then randomized to receive Pancreaze at doses of either 375, 750, 1,125 or 1,500 lipase units/kg of body weight per meal for 5 days. Patients showed similar control of fat malabsorption at the end of the run-in period as at the end of the trial across the four dose groups.

Safety

Delayed and immediate release formulations of porcine-derived PEPs used to treat exocrine pancreatic insufficiency have been generally well tolerated. The most common adverse events reported relate to the patients' underlying disease and are referable to the gastrointestinal tract. Pancreatic enzyme products are not absorbed from the gastrointestinal tract and are not systemically active.

Risk of Fibrosing Colonopathy. Fibrosing colonopathy, a rare, serious condition which can lead to colonic stricture, has been reported following treatment with high doses of pancreatic enzyme products, usually over a prolonged period of time and most commonly in pediatric patients with cystic fibrosis. 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. Patients receiving doses higher 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. At approval, a Medication Guide will be required as part of a REMS for Pancreaze (pancrelipase) Delayed-Release Capsules that will inform patients of this risk.

Potential for Irritation to Oral Mucosa. Care should be taken to ensure that Pancreaze is not retained in the mouth. Pancreaze should not be crushed or chewed or mixed with foods having a pH greater than 4.5 since these actions can disrupt the enteric coating and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Potential Viral Exposure to Patients from the Product Source. Like other porcine-derived PEPs, Pancreaze is derived from porcine pancreas tissue obtained as a by-product from the slaughter of pigs as a source of food. Audit procedures are in place to ensure that the pancreas raw material is derived from pigs certified as fit for human consumption and to ensure that legal requirements regarding e.g., hygienic factors, health certification of slaughtered animals, and surveillance for animal diseases are met. Two broad categories of porcine viruses, enveloped and non-enveloped viruses, may be transmissible to humans (i.e., have zoonotic potential). In addition, viruses with zoonotic potential such as HEV, the causative agent for hepatitis E, have recently emerged in pigs. Manufacturing processes appear to inactivate most

¹ See <http://www.fda.gov/cder/guidance/6275fnl.htm>

enveloped viruses that could be present in the drug substance but have limited capacity to inactivate non-enveloped viruses.

Although there has been no documentation of viral transmission to humans, FDA's Anti-Viral Advisory Committee concluded that there was a theoretical risk of transmission of viral disease to patients treated with porcine-derived PEPs, including Pancreaze (pancrelipase) Delayed-Release Capsules. At approval, a Medication Guide will be required as part of a REMS for Pancreaze that will inform patients of this theoretical risk. In addition, the applicant will be required to conduct a 10-year observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancreaze. The applicant has also agreed to several postmarketing commitments to ensure that the manufacturing process effectively controls viral load (see below).

Risk of Hyperuricemia. Porcine-derived PEPs contain purines that may increase blood uric acid levels. Caution should be exercised when prescribing Pancreaze to patients with gout, renal impairment, or hyperuricemia.

Risk of Severe Allergic Reactions. Rarely, severe allergic reactions including anaphylaxis, asthma, hives, and pruritus, have been reported in patients with a known allergy to proteins of porcine origin who are treated with PEPs.

Chemistry, Manufacturing and Controls Considerations

Pancreaze Delayed-Release Capsules contain either 4,200, 10,500, 16,800 or 21,000 USP units of lipase. The capsules contain beads that are enteric-coated to minimize destruction or inactivation in gastric acid. Pancreaze is designed to release most of the enzymes *in vivo* at pH greater than 5.5. The drug substance is manufactured by Nordmark, the Drug Master File (DMF) holder (DMF #7090), and is the same as that for Zenpep Delayed-Release Capsules (Eurand's pancreatic enzyme product under NDA 022210) which was approved in August 2009. The drug product is also manufactured by Nordmark; all pertinent information related to the drug product has been submitted to NDA 022523 rather than to the DMF.

The following postmarketing commitments involve the drug substance: 1) develop and validate an infectious assay for PCV1, 2) establish lot release specifications for PCV1, 3) perform additional monitoring of viral load entering the manufacturing process; the control program will include monitoring for human pathogenic viruses by qPCR, and 4) improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Assays will be revised and assay validation data will be submitted together with acceptance criteria.

The following postmarketing commitments involve the drug product: 1) initiate and complete the proposed studies 04020298 and 04020299 that evaluate the stability of Pancreaze under conditions of use, and 2) re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the Pancreaze manufacturing process. After 50 lots of low-potency microtablets and 25 lots of high-potency microtablets are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability.

Clinical Pharmacology

Pancreatic enzymes are not absorbed from the gastrointestinal tract in any appreciable amount. For this reason, a thorough QT assessment for this product was not requested.

Pediatric Considerations

Pediatric Use. The Use in Specific Populations section, **Pediatric Use** subsection, will state that the short-term safety and effectiveness of Pancreaze were demonstrated in two clinical studies in patients with cystic fibrosis aged 6 to 30 months, and 8 to 17 years, respectively. In addition, the label will state that "The safety and efficacy of pancreatic enzyme products with different formulations of pancrelipase

consisting of the same active ingredients (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience.”

For infants 12 months of age or less, or older individuals who cannot swallow capsules, the contents of the capsules may be sprinkled into the mouth or mixed in a small amount of soft, acidic food such as applesauce. Although PEPs, including Pancreaze, are not approved for administration via gastrostomy tubes, a small number of patients may require PEPs to be given through this route. The applicant has committed to conducting *in vitro* testing to evaluate the feasibility of administering Pancreaze via gastrostomy tubes.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant has fulfilled the pediatric study requirement for ages 1 year to 17 years for this application. We are waiving the pediatric study requirement for ages birth to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed before 1 month of age, so there would not be enough patients in this age range to study. The pediatric study requirement for 1 month to 1 year is not fulfilled due to the lack of an age appropriate formulation.

At this time, we are deferring submission of an age appropriate formulation that will allow for dosing to the youngest, lowest weight 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.

Postmarketing Requirements under 505(o)

Section 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 holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following serious risks associated with the use of Pancreaze and other porcine-derived pancreatic enzyme products (PEPs): the known serious risk of fibrosing colonopathy with higher doses of PEPs and the unexpected serious risk of transmission of viral disease to patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct the following studies:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pancreaze (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.
2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancreaze (pancrelipase) Delayed-Release Capsules.

Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of FDAAA amends the 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)).

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

The details of the REMS requirements were outlined in a REMS notification letter to the applicant dated September 24, 2009. The applicant's proposed REMS, submitted on April 12, 2010, will be analogous to REMS for other approved porcine-derived PEPs, and will consist of a Medication Guide and a timetable for submission of assessments of the REMS.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "Pancreaze" is acceptable.

Julie Beitz, MD
Director,
Office of Drug Evaluation III
CDER, FDA

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22523

ORIG-1

JOHNSON &
JOHNSON
PHARMACEUTICA
L RESEARCH &
DEVELOPMENT
LLC

Pancrelipase Microtablets

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
04/12/2010