

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-210**

**OFFICE DIRECTOR MEMO**

**MEMORANDUM**

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

DATE: August 27, 2009  
FROM: Julie Beitz, MD  
SUBJECT: Office Director Memo  
TO: NDA 022210 Zenpep (pancrelipase) Delayed-Release Capsules  
Eurand Pharmaceuticals Inc.

**Summary**

Zenpep (pancrelipase) Delayed-Release Capsules is 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). While there is no previous marketing experience with Zenpep, several PEPs have been marketed in the US for many years since pre-Drug Efficacy Study Implementation (DESI, pre-1962) 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 Zenpep (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency in patients with cystic fibrosis and other conditions. All previously identified deficiencies have either been resolved or will be addressed post-approval. There are no inspectional issues that would preclude approval of the application at this time.

**Dosing**

Zenpep (pancrelipase) Delayed-Release Capsules is 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. Zenpep 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.

Zenpep (pancrelipase) Delayed-Release Capsules is not comparable to or interchangeable with other PEPs. The active pharmaceutical ingredient for all PEPs, including Zenpep, 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 Zenpep labeling will state that "Zenpep is not interchangeable with any other pancrelipase product."

**Regulatory History**<sup>1</sup>

---

<sup>1</sup> Additional information regarding the regulatory history of NDA 022210 may be found in the review of Daniel Shames dated June 16, 2008.

On December 17, 2007, Eurand submitted NDA 022210 and was granted a priority review. FDA took an approvable action on June 16, 2008 due to deficiencies in two areas: a) chemistry, manufacturing and controls, and b) clinical pharmacology. In addition, FDA's letter stated that prior to approval, an acceptable facility inspection would be required. At the same time, FDA notified Nordmark Arzneimittel GmbH & Company, KG, the holder of DMF # 7090 in support of Eurand's NDA, in writing of several deficiencies in chemistry, manufacturing and controls regarding the drug substance. Nordmark was requested to address these deficiencies and submit an amendment to their DMF.

The current NDA submission, dated December 22, 2008, received on December 23, 2008, represents a complete response to FDA's approvable letter. Additional information submitted by Nordmark to their DMF was also reviewed. A safety update, submitted June 15, 2009, was considered a major amendment and extended the review clock to September 21, 2009. 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 Zenpep (pancrelipase) Delayed-Release Capsules.

### **Efficacy**

As with other PEP manufacturers, Eurand was requested to perform at least one controlled clinical trial with Zenpep 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*.<sup>2</sup> Eurand conducted two clinical trials. One was a randomized, double-blind, placebo-controlled crossover trial in 34 patients, ages 7-23 years (including 26 patients with ages 7-17), with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were randomized to either Zenpep or matching placebo for 6-7 days, followed by crossover to the alternate treatment for an additional 6-7 days. The Zenpep dose during the controlled treatment periods ranged from a mean of 3900 to 5700 lipase units/kg of body weight per day. All patients consumed a high fat diet. Zenpep treatment was associated with significantly improved fat absorption compared to placebo when measured as the mean coefficient of fat absorption in 72-hour stool samples ( $p < 0.001$ ). There were similar responses to Zenpep by age and gender.

The second was an uncontrolled trial in 19 pediatric patients ages 1 to 6 years (mean age 4 years) with exocrine pancreatic insufficiency due to cystic fibrosis. Patients were transitioned from their usual PEP treatment, without a washout period, to Zenpep at individually titrated doses ranging between 2300 and 10,000 lipase units/kg of body weight per day for 14 days. Patients showed similar control of fat malabsorption measured by spot fecal fat testing when switched to Zenpep treatment.

### **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 Zenpep (pancrelipase) Delayed-Release Capsules that will inform patients of this risk.

**Potential for Irritation to Oral Mucosa.** Care should be taken to ensure that Zenpep is not retained in the mouth. Zenpep should not be crushed or chewed or mixed with foods having a pH greater than 4.5 since

---

<sup>2</sup> See <http://www.fda.gov/cder/guidance/6275f1n1.htm>

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.

**Risk of Transmission of Viral Disease to Patients.** Like other porcine-derived PEPs, Zenpep 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 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 Zenpep (pancrelipase) Delayed-Release Capsules. At approval, a Medication Guide will be required as part of a REMS for Zenpep that will inform patients of this theoretical risk. In addition, the applicant has 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 Zenpep 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**

Zenpep capsules contain 5,000, 10,000, 15,000 or 20,000 USP units of lipase. The capsules contain beads that are enteric-coated to minimize destruction or inactivation in gastric acid. Zenpep is designed to release most of the enzymes *in vivo* at pH greater than 5.5.

The information submitted by Eurand and Nordmark addressed many of the deficiencies that had been previously identified by FDA. The remaining deficiencies do not preclude approval and can be addressed as postmarketing commitments. These include: 1) tightening acceptance criteria for the drug product amylase and protease potency assays, 2) developing and validating an infectious assay for PCV1 for the drug substance, 3) establishing lot release specifications for PCV1, PCV2 and PPV for the drug substance, 4) additional monitoring for enveloped viral load entering the manufacturing process, 5) improving the sensitivity of qPCR assays used for drug substance release testing to detect EMCV, HEV, PEV9, Reo 1/3, Rota A, Influenza A, VSV-IND, and VSV-NJ viruses, 6) assessing the risk to product quality associated with porcine hokovirus, and submitting a control strategy for mitigating this risk to product quality, 7) improving the animal surveillance program and risk assessment evaluation for source animals to capture new and emerging viral adventitious agents, and 8) assigning an expiration date to the label for the pancrelipase drug substance used to produce the Zenpep drug product.

### **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. Eurand has adequately addressed the clinical pharmacology deficiency in FDA's June 2008 approvable letter.

### **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 “Zenpep” is acceptable.

### **Pediatric Considerations**

**Pediatric Use.** The **Use in Special Populations** section, **Pediatric Use** subsection, will state that the short-term safety and effectiveness of Zenpep were demonstrated in two clinical studies in patients ages 1 to 17 years with cystic fibrosis. 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.”

**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.

Eurand 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 0 months to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed below 1 month of age, and the small number of patients diagnosed in this age category and their geographic dispersal would make conduct of a study in this age group highly impracticable. 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. Submission of a supplement is expected by December 31, 2010.

### **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 Zenpep 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 Eurand 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 Zenpep (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 Zenpep (pancrelipase) Delayed-Release Capsules.

**Risk Evaluation and Mitigation Strategy (REMS) Requirements**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (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 Zenpep (pancrelipase) Delayed-Release Capsules, to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with high doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

Eurand's proposed REMS, submitted on August 10, 2009, and amended on August 14, 2009, will be analogous to REMS for other porcine-derived PEPs, and will consist of a Medication Guide and a timetable for submission of assessments of the REMS.

---

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22210	ORIG 1	EURAND PHARMACEUTICA LS LTD	ZENTASE
NDA 22210	ORIG 1	EURAND PHARMACEUTICA LS LTD	ZENTASE

---

**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  
08/27/2009