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APPLICATION NUMBER:

22-210

SUMMARY REVIEW

Division Director Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA #	22-210
Applicant Name	Eurand Pharmaceuticals, Inc.
Date of Submission	December 22, 2008; Received December 23, 2008
PDUFA Goal Date	September 23, 2009
Proprietary Name / Established (USAN) Name	Zenpep pancrelipase
Dosage Forms / Strength	Delayed release capsules for oral administration Zenpep 5,000 lipase/17,000 protease/27,000 amylase Zenpep 10,000 lipase/34,000 protease/55,000 amylase Zenpep 15,000 lipase/51,000 protease/82,000 amylase Zenpep 20,000 lipase/68,000 protease/109,000 amylase
Proposed Indication(s)	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Marjorie Dannis, MD/ Anne Pariser, MD/Anil Rajpal, MD
Statistical Review	Freda Cooner, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/Sushanta Chakder, PhD
CMC Review/OBP Review	Howard Anderson, PhD/Emanuela Lacana, PhD/Gibbes Johnson, PhD/Barry Cherney, PhD. Virology reviewer: Ennan Guan, PhD
Microbiology Review	Stephen Langille, PhD/James McVey
Clinical Pharmacology Review	Tien-Mien Chen, PhD/Sue-Chih Lee, PhD
DDMAC	Shefali Doshi/Kathleen Klemm
DSI	Khairy Malek/Constance Lewin, MD, MPH
CDTL Review	Anil Rajpal, MD (Anne Pariser, MD first cycle)
OSE/DMEPA	Deveonne Hamilton-Stokes, RN, BSN/Todd Bridges, RPh/Denise Toyer, PharmD/Carol Holquist, RPh
OSE/DRISK	Jessica M Diaz, BSN, RN/Robin Duer, RN, MBA/ Claudia Karwoski, PharmD/ Jodi Duckhorn, MA
SEALD	Jeanne Delasko, RN, MS/Laurie Burke

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Division Director Review

DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
DRISK = Division of Risk Management
SEALD = Study Endpoints and Labeling Development Team

Division Director Review

1. Introduction

Zenpep is an enteric-coated, delayed-release, porcine-derived pancreatic enzyme. This NDA is a complete response to a first cycle review Approvable letter sent June 16, 2008. The resubmission was received by FDA on December 23, 2008. A safety update submitted on June 15, 2009 extended the PDUFA date 3 months.

The deficiencies identified in the first review cycle were related to chemistry, manufacturing, and clinical pharmacology. There were no specific clinical deficiencies identified during the first review cycle. Viral issues associated with porcine derived pancreatic enzyme products were discussed at the December 2, 2008 meeting of the Anti-viral Advisory Committee, in the context of the discussion of the safety and efficacy of the pancrelipase product, Creon. The FDA has concluded that porcine derived pancreatic enzyme products should have a Medication Guide to inform patients of both the theoretical risk of transmission of a viral disease to patients from these products and the potential risk of fibrosing colonopathy.

My review summarizes the major review conclusions of each review discipline.

2. Background

Pancreatic enzyme products (PEPs) are used to treat exocrine pancreatic insufficiency. The most common causes of pancreatic insufficiency are cystic fibrosis and chronic pancreatitis. The predominant clinical manifestations are secondary to fat malabsorption - steatorrhea, abdominal pain and weight loss.

PEPs have been available since prior to the Federal Food, Drug and Cosmetic Act of 1938. They have been marketed without being subject to FDA review. They are derived from pancreas glands harvested from pigs raised for human consumption. Variation in the formulations and manufacturing processes result in variations in drug potency across products and within individual products. PEPs are not interchangeable. The historic lack of manufacturing controls raised concerns regarding product quality, both from a safety and efficacy standpoint. Beginning in 1979 the FDA published a series of notices in the Federal Register that culminated with the 2004 Notice of Requirement for NDA Approval, which stated PEPs must obtain NDA approval within 4 years from the published notice in order to be legally marketed. The *Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs* was published in 2006. In October 2008 a Notice of Extension of the deadline for approval under NDA was published. It stated that manufacturers must have an open IND for their PEP product by April 28, 2008, and an approved NDA by April 28, 2010.

Currently the only approved PEP products are Cotazym, an immediate release PEP that is not marketed in the US, and Creon, a delayed-release PEP approved on April 30, 2009. Creon was approved after it was discussed at the December 2, 2008 meeting of the Anti-viral Advisory Committee. During that meeting viral issues associated with porcine-derived pancreatic enzyme products were discussed. In light of the discussions of the Advisory Committee, the FDA concluded that PEPs should have a Medication Guide both to inform patients of the risk of fibrosing colonopathy (which may be increased with high dose exposures to pancreatic enzyme products) and the risk of transmission of a viral disease from these products. Creon was approved with a Risk Evaluation and Mitigation System (REMS) with Medication Guide.

3. CMC

Zenpep capsules contain 5,000, 10,000, 15,000 and 20,000 USP units of lipase. The capsules contain beads (or “mini tablets”) that are coated to produce the delayed release characteristics of the product, intended to assure that the enzymes “survive” exposure to gastric acid and are released in the higher pH environment of the small bowel.

The drug substance is manufactured by Nordmark Arzneimittel GmbH and Company, which is the Drug Master File (DMF) holder. The drug product is manufactured by Eurand. The porcine pancreas glands are obtained from slaughterhouses in the US and Canada. There are (b) (4) viral inactivation steps in the drug substance manufacturing process: (b) (4)

In the original review cycle the Product Reviewer noted deficiencies in both the drug substance and drug product. (b) (4)

(b) (4) The Virology Reviewer noted that the manufacturing process for the drug substance does not inactivate non-enveloped viruses, and additional data were needed to assure that the manufacturing process provided acceptable viral inactivation of enveloped viruses. Nordmark’s routine viral testing plan was found not to be adequately comprehensive, and needed to be extended to include all viruses with the capacity to infect humans and address risk mitigation for emerging viruses. The reviewers requested further information on validation of the PCR tests and viral infectivity assays used.

The drug product deficiencies identified in the first review cycle were related to: (1) process validation; (2) enteric coating; (3) stability data; (4) storage conditions; (5) olive oil qualification; (6) drug product acceptance criteria; (7) RP-HPLC assay validation; (8) qualification of the reference standard; and (9) use of the USP lipase reference standard.

The Microbiology reviewer recommended an approval action in the first cycle. The reviewer noted that the product was non-sterile, but had acceptable microbial limits release specifications for total bacteria, yeasts and molds. Salmonella and E. coli species are absent.

I concur with the conclusions of the Product Reviewers that the deficiencies associated with both the drug substance and drug product identified during the initial review cycle (and described in the June 16, 2008 Approvable letter and a June 13, 2008 Information Request

letter to the DMF holder) have been adequately addressed in this resubmission. With regard to the specific deficiencies identified in the first cycle drug substance review, the Product Reviewer stated in his review that the DMF has “significantly improved the product quality standard for the pancrelipase API.....The recent updates to [the DMF] have improved the potency reference standard qualification program, provided the results of recent successful process validation studies, and tightened the acceptance criteria for the RP-HPLC identity/purity test.” He noted that there is now an adequate risk mitigation plan for adventitious agents. He recognized that non-enveloped viruses aren’t inactivated by the manufacturing process, but Nordmark has “developed and validated assays to monitor for porcine virus known to have the potential to cause human infections.” The manufacturer implemented a PCR method to test for HEV and will reject lots in which HEV is detected. Critical validation parameters (e.g., specificity, robustness, limit of detection) were provided for infectious assays for PPV and PCV2.

The Product Reviewers recommend approval of this NDA and I concur. They note that the remaining deficiencies do not preclude approval and can be addressed as PMCs. One PMC relates to drug product and others relate to drug substance. The following post-marketing commitments have been agreed to by the Applicant and the DMF holder:

1. Reevaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the manufacturing process. After 50 drug product lots are manufactured, specifications will be reevaluated and adjusted to reflect manufacturing history and capability.
2. Develop and validate an infectious assay for PCV1.
3. Establish lot release specifications for PCV1 for the drug substance.
4. Establish lot release specifications for PPV and PCV2 for the drug substance.
5. Perform additional monitoring of enveloped viral load entering the manufacturing process. The control program will include the selection of human pathogenic enveloped viruses for monitoring by qPCR together with an appropriate control strategy.
6. 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. Revise the assays, and submit assay validation data, together with acceptance criteria.
7. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.
8. Improve the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program will include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.
9. Assign an expiration date to the label of the pancrelipase drug substance used for production of the Zenpep product. An expiration date will be included on the drug substance label by December, 2009.

I concur with the conclusions of the product reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The remaining review issues can be appropriately addressed as PMCs.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The pharmacology reviewers recommended approval in the first review cycle, but recommended labeling revisions in the Pregnancy section of the label and in the Carcinogenesis, Mutagenesis and Impairment of Fertility section. Those recommendations were incorporated during labeling negotiations in this cycle.

5. Clinical Pharmacology/Biopharmaceutics

In the first review cycle the Clinical Pharmacology reviewers evaluated an *in vivo* intubation study designed to evaluate the bioavailability of Zenpep in patients with exocrine pancreatic insufficiency. Gastric and duodenal aspirates were tested under fed condition. The reviewers concluded that the study results of the *in vivo* intubation study couldn't be interpreted. This study was not, however, required for NDA approval.

In addition, the Clinical Pharmacology reviewers evaluated an *in vitro* stability study that examined Zenpep's stability when mixed with 10 types of food with pH<5.0. Some of the results of the *in vitro* stability study were questioned during the first cycle review, but were not considered approvability issues. The need for clarifying information to address this question was communicated to the Applicant in the Approvable letter. The errors detected in the initial review were corrected in the resubmission and the data from the *in vitro* stability study were used to support product labeling for opening the Zenpep capsules to sprinkle the product on certain acidic foods when patients are unable to swallow capsules. Patients will be instructed in the Medication Guide that when the product is mixed with commercially prepared acidic foods it should be taken immediately after mixing.

I concur with the clinical pharmacology/biopharmaceutics reviewer's conclusion that there are no outstanding clinical pharmacology issues that preclude approval of Zenpep at this time.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this application because Zenpep is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

The clinical efficacy studies submitted to support product approval were reviewed in the first review cycle. The clinical reviewers concluded that the efficacy findings support approval and labeling of Zenpep for treatment of steatorrhea due to exocrine pancreatic insufficiency from cystic fibrosis or other causes.

The FDA’s Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs states that “Although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea.” One of the examples of an acceptable pharmacodynamic measure provided in the Guidance is “Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection.” The major study submitted to this NDA utilized the pharmacodynamic measure coefficient of fat absorption (CFA).

There were two efficacy studies submitted for review. One was a randomized, placebo-controlled trial and the other was an open label study. In the “pivotal” study (EUR-1008-M), 34 patients ages 7 to 23 years were randomized to receive Zenpep or matching placebo. After 6 -7 days of treatment, patients were crossed over to the alternate treatment for an additional 6-7 days. Zenpep was administered in a dose range consistent with the recommendations of the Cystic Fibrosis Foundation Consensus Guidelines. The primary efficacy comparison was the difference in mean CFA between the Zenpep and placebo periods. The summary results are shown in the table below, which is reproduced from Dr. Anil Rajpal’s CTDL review. The mean CFA difference between Zenpep and placebo was 25% (p<0.001; 95% CI [-32,-19]).

ANOVA Model Results of CFA (%) [Study EUR-1008-M](Table reproduced from Table 4 in the CDTL review, which was also presented in the CDTL review in the original review cycle)

	Zenpep (N=32)	Placebo (N=31)
Mean (SEM)	88.3 (1.4)	62.7 (3.4)
SD	7.9	19.1
Median	89.8	65.8
Min, Max	62.9, 98.7	28.7, 95.5
LS means (SEM)	88.3 (2.6)	62.8 (2.66)
Difference between Zenpep and Placebo		-25.5
95% CI		(-31.7, -19.3)
p value		<0.001

The biostatistical reviewer suggested that in light of the crossover design of the study, a paired t-test by each subject might be considered the more conventional analysis of these data. The t-test results of CFA were consistent with the results from the ANOVA model and the reviewer noted that “the significance difference between two treatment effects can still be concluded.”

The open label, non-randomized second study, which enrolled children under the age of 7, was only considered a supportive study (EUR-1009-M). Children were transitioned to Zenpep from their usual PEP treatment, without a wash-out period, after a 4-14 days screening period (during which they continued to take their usual PEP formulation). This study design was utilized based on recommendations of the Cystic Fibrosis Foundation that placebo-controlled trials or washout periods are not appropriate when studying treatments of fat malabsorption in young children with cystic fibrosis. The primary endpoint was percentage of responders after 1-2 weeks of treatment. Responders were defined as patients without steatorrhea (spot fecal fat <30%) AND without signs and symptoms of malabsorption. The signs and symptoms

assessed for the primary endpoint analysis were stool consistency (presence of oil/grease/blood), pain, bloating and flatulence. These symptoms were recorded in a diary.

For the non-patient reported component of the primary endpoint, percentage of fecal fat, the clinical reviewers noted that during screening 14/19 patients had a fecal fat <30%. After transition to Zenpep at completion of a dose stabilization period, 13/19 patients had a fecal fat <30%, and at end of study 13/18 patients had a fecal fat <30%. The reviewers concluded these data are supportive of the efficacy of Zenpep. When patient reported symptoms of malabsorption were included in the responder definition, the number of responders was 13 after dose stabilization and 11 at study completion. Ten patients met the responder definition at screening while taking their usual PEP.

There is no previous clinical experience with the formulation of Zenpep studied in these clinical trials. There is substantial information in the medical literature on clinical experience with formulations of porcine-derived PEPs.

I concur with the reviewers that the data submitted in the NDA support approval of Zenpep for treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis or other causes. I concur with the reviewers' recommendations to include information on both clinical studies in product labeling, with the primary emphasis placed on the randomized, placebo-controlled study in patients over the age of 7 years. The second study utilized a less robust endpoint, spot fecal fat, and was not a randomized, controlled study. This study has been included in Section 14 Clinical Studies of the product label and Section 8.4 Pediatric use, but is qualified with language that describes its open-label, uncontrolled design. Specific data from this study were not included in the label, in either Section 14 or Section 8.4.

8. Safety

In the initial review cycle, the adverse event profile of Zenpep observed in the individual studies described above was consistent with the adverse event profile of PEPs in the medical literature. The adverse events observed reflected underlying disease. The most commonly reported adverse events were gastrointestinal and respiratory events. No new adverse events were noted in the safety update submitted in the resubmission.

A summary of adverse reactions observed in the placebo-controlled "pivotal" trial was included in the Adverse Reactions - Clinical Trials Experience section of the label (Section 6.1). In addition, the reviewers recommended inclusion of a description of the adverse reactions observed in the open-label single-arm study that enrolled patients ages 1 to 6 years.

The medical literature identifies the following safety concerns related to use of PEPS, which were incorporated in the label under Section 5 Warnings and Precautions:

- a. Fibrosing colonopathy, a rare condition that may result in colonic stricture, has been associated with high dose exposure to PEPs, but the etiology is uncertain. Most cases have been reported in younger children with CF. The Cystic Fibrosis Foundation

(CFF) Consensus Guideline recommend limiting the maximum daily dose of PEPs, not to exceed 10,000 lipase units/kg/day or 2,500 lipase units/kg/meal.^{1,2,3}

- b. Irritation to oral mucosa by PEPs results from disruption of the enteric coating, which allows early release of the enzymes in the mouth.
- c. Hyperuricemia/Hyperuricosuria associated with PEPs may be due to absorption of porcine purines.
- d. There is a theoretical risk of viral transmission from PEPs because they are porcine-derived products. Although there may be a risk of porcine viruses being transmitted to humans through PEPs, no viral illness secondary to PEP exposure has been documented. Procedures have been put in place in the manufacturing process to minimize this risk (e.g., certificates of health of animals, acceptance criteria, viral load testing, viral inactivation studies, and surveillance for animal diseases).
- e. Hypersensitivity reactions have been reported with PEPs.

Based on concerns that exceeding the recommended dose of PEPs can increase the risk of developing fibrosing colonopathy and given the theoretical risk of viral transmission from PEPs, the reviewers recommended that Zenpep be approved with a REMS (Risk Evaluation and Mitigation Strategy) with Medication Guide. They also recommended two post-marketing safety studies as PMRs (Post Marketing Requirements). I concur with their recommendations. The REMS with Medication Guide and the PMRs are consistent with those that were conditions of approval of Creon. The reviewers collaborated with reviewers from OSE/DRISK in evaluating the REMS and the Medication Guide. Eurand submitted the approved REMS on August 10, 2009. It was amended on August 14, 2009. It consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The postmarketing required studies under 505(o) are:

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.

¹ Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *J Pediatric Gastroenterology and Nutrition*. 2002. 35:246-259.

² Borowitz, D, Grand RJ, Durie PR, and the Consensus Committee, Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, *J Pediatrics* 1995; 127:681-684.

³ FitzSimmons SC, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *NEJM* 1997; 336:1283-1289.

9. Advisory Committee Meeting

There was no Advisory Committee meeting to discuss this application. However, the review decisions regarding labeling and the Medication Guide were influenced by the Committee deliberations at the December 2, 2008 Antiviral Advisory Committee meeting for Creon, in which the potential viral transmission issues related to porcine derived pancreatic enzyme products were discussed.

10. Pediatrics

A brief description of the efficacy results from the open-label single-arm study that enrolled patients between the age of 1 and 6 years was included in Section 8.4 Use in Specific Populations – Pediatric Use of the product label. A description of the results in the pediatric subpopulation (i.e., ages 7 to 17 years) of the double-blind placebo-controlled trial was also included in this section of the label. For the pediatric subpopulation of the randomized, placebo controlled study, Section 8.4 states “The safety and efficacy in pediatric patients in this study were similar to adult patients.” Section 8.4 also refers to the evidence of safety and efficacy of PEPs with different formulations of pancrelipase in the medical literature, and states that dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences.

Both studies were also described in Section 14 Clinical Studies of the product label, but the description of the open label trial that enrolled children less than 7 years of age was qualified with language that clearly outlined the limitations of this small study – it’s open-label and uncontrolled design. Specific data from this study are not provided in either Section 14 or Section 8.4 of the label.

The safety data from the pediatric subpopulation of the randomized, placebo controlled study is summarized in the Adverse Reaction 6.1 Clinical Trials Experience section of the label by the statement, “The type and incidence of adverse events were similar in children, adolescents and adults”. The safety data from the open label study is qualified by pointing out there was no comparator arm. The label states that the adverse events observed in this small study “were similar in type and frequency to those reported in the double-blind, placebo-controlled trial.”

This application was presented to the Pediatric Research Committee (PeRC) on May 6, 2009. The Approval letter will state that we are waiving the pediatric study requirement for ages birth to 1 month because necessary studies are impossible or impracticable (because patients are usually not diagnosed before the age of 1 month, so there would not be enough eligible patients in this age range to study). We are deferring submission of an age appropriate formulation. The pediatric study requirements have been fulfilled for ages 1 year to 17 years. (The pediatric requirement for 1 month to 1 year is not fulfilled due to the lack of an age appropriate formulation.) Published data in the literature establish the safety and efficacy of PEPs in general for treatment of children with exocrine pancreatic insufficiency.

11. Other Relevant Regulatory Issues

In the original review cycle of this NDA, the Division of Scientific Investigations (DSI) conducted site inspections of two clinical sites and the central laboratory from the randomized,

placebo controlled trial. The overall assessment was that the data were reliable and could be used in support of the NDA.

The clinical reviewer evaluated the financial disclosure forms during the first review cycle and all but one investigator who participated in the three clinical studies reported no financial interests. The only investigator who reported receiving payments from Eurand was an investigator in the bioavailability study. The clinical reviewer determined that there were no reported financial interests that would affect the overall study results of the randomized, placebo-controlled “pivotal” trial and the supportive open label pediatric study.

There are no unresolved relevant regulatory issues.

12. Labeling

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the name “Zenpep” acceptable from a promotional perspective. The DMEPA reviewers also found the name acceptable.

The Applicant was asked to revise the label and Medication Guide to be consistent with the corresponding sections of labeling for the recently approved PEP, Creon.

The recommendations from the DMEPA Labeling Review, the DRISK Proposed REMS Review, the DRISK Patient Labeling and Medication Guide Review, the DTP Carton and Container Label Review, the DDMAC Labeling Review, and the SEALD Labeling Review were incorporated in the label negotiations.

The capsules are packaged in bottles containing 100 capsules or 500 capsules; each bottle contains one desiccant unit. Because of the concern that capsules may be dispensed without the desiccant, the outer carton and container labeling was revised to indicate that the container is a unit of use container with the language “Pharmacist: Dispense in original container”.

See also the specific descriptions of labeling summarized in other sections of this review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval for the indication “for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions”.
- Risk Benefit Assessment – All disciplines have determined that there are no issues that preclude approval of this product at this time. The risk and benefit characteristics of this product are favorable, and I concur with the reviewers’ recommendations that this product should be approved with the REMS described below and the PMRs and PMCs described below.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies -

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 submitted the REMS August 10, 2009 and it was amended August 14, 2009. It consists of a Medication Guide and the following timetable for submission of assessments of the REMS. (Further details about the REMS assessment plan can be found in the Approval Letter.)

1st Assessment: (March 23, 2011) 18 months after NDA approval

2nd Assessment: (September 23, 2012) 3 years after NDA approval

3rd Assessment: (September 23, 2016) 7 years after NDA approval

- Recommendation for other Postmarketing Requirements and Commitments

The approval letter will contain the following Postmarketing Required Studies under 505(o) to address important safety issues associated with PEPs:

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.

Final protocol: July 15, 2010

Study completion date: July 1, 2022

Final report: December 31, 2022

2. 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Zenpep (pancrelipase) Delayed-Release Capsules.

Final protocol: July 15 2010

Study completion date: July 1, 2022

Final report submission: December 31, 2022

In addition, under PREA, the applicant is required to develop an appropriate pediatric formulation for the youngest clinically affected age groups. That requirement is deferred and is:

3. 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. Submit a supplement for an age appropriate formulation by December 31, 2010.

The Applicant has also agreed to Post-Marketing Study Commitments, all related to chemistry/manufacturing of the drug substance and drug product. The list of those commitments and the timelines for final report submissions can be found in the Approval letter.

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/s/

DONNA J GRIEBEL
08/27/2009