Clinical Pharmacology Review

NDA:	22-210
Proposed Brand Name:	Zenpep
Generic Name:	Pancrelipase
Dosage form and Strength:	Enteric-coated minitablets (or beads) in capsules; 5,000, 10,000, 15,000 and 20,000 lipase units/capsule
Route of administration:	Oral
Indication:	Replacement therapy in patients with partial or complete exocrine pancreatic insufficiency
Sponsor:	Eurand
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology and Inborn Error Products (HFD-180)
OCP Division:	DCP III
Submission date:	01/09/09
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

NDA 22-210 for Zenpep has been reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, the NDA is acceptable provided that a mutual agreement on labeling language can be reached between the sponsor and Agency.

1.2 General Comments

The bioavailability study is currently not required for the NDA approval because many challenges in the study design and study conduct remain to be overcome before the study can be used reliably to assess the bioavailability of pancreatic enzyme products. As such, the sponsor's study results will not be reflected in the label.

1.3 labeling Comments

Labeling comments on page 5 need to be conveyed to the sponsor.

1.4 Phase IV Commitments: None

1.5 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

The original NDA 22-210 for Zenpep (Pancrelipase) capsules was submitted by Eurand on 12/14/07. In the Clinical Pharmacology and Biopharmaceutics section, two studies were submitted: 1) an *in vivo* intubation study (No. PR-001) and 2) an *in vitro* compatibility study to evaluate the stability of pancreatic enzymes following mixing of the Zenpep capsule contents with a variety of acidic foods. The above two studies were found not acceptable in the original review. The deficiencies related to the *in vivo* intubation study was considered not an approval issue. Therefore, the FDA's approvable letter dated 6/16/08 included only the comment related to the *in vitro* compatibility study.

Bioavailability study (Intubation Study)

After the submission of the original NDA on 12/14/07, the sponsor continued to enroll patients to study PR-001. The amended study report was submitted on 01/09/09, which includes data from a total of 17 patients, i.e., the original 11 patients and an additional 6 patients enrolled subsequently. Out of the 17 patients, six were excluded from the final analysis. (b) (4)

(b) (4)

(Reviewer's Comments:

1. (b) (4)

4. Based on the data provided, the reliability of the study cannot be assured. As such, the study results will not be reflected in the label. However, as stated before, the bioavailability study is not required for the NDA approval.

(b) (4)

(b) (4)

In Vitro Compatibility Study

The Agency's approvable letter dated 06/16/08 included a comment regarding the errors found in the *in vitro* stability study report as shown below.

"In an Information Request letter sent on February 15, 2008, we requested clarification of the *in vitro* stability data you provided in the July 31, 2007, submission (Module 3, Section 3.2.P.2.2 Drug Product, pp. 91-100). In your submission, you evaluated the *in vitro* stability of pancrelipase after the capsules were opened and the contents were mixed with various types of food. You provided the stability data for three batches of EUR-1008 capsules; however, we noted that the individual data for two of the three batches were identical. It is not clear to us whether these are the actual results, or whether there were errors in the dataset. Provide clarification on the stability data as part of your complete response."

The sponsor, however, found the errors before then and submitted the revised table on 6/9/08 in their response to other CMC information requests. The revised results are shown in Table 4.

Table 4. *In Vitro* Compatibility between Zenpep Capsule Contents and Several Types of Food: Recovery of Lipase 60 minutes after mixing

Batch Nos.	USP Dissolution Part 2 (pH 6.0 for 30 min)		
	P200550387	P200550348	P200550668[1]
Food Type	Mean (CV) % dissolved[2]		
Applesauce Mott's	100 (1.5)	94 (1.0)	92 (3.0)[2]
Applesauce Gerber	98 (1.5)	97 (1.6)	89 (1.2)
Bananas	99 (1.1)	91 (1.1)	89 (3.0)
Pear	99 (1.8)	99 (2.8)	98 (2.8);
Pudding Vanilla/Apples	102 (2.7)	96 (1.0)	91 (1.0)
Banana Pudding	102 (2.5)	95 (1.6)	91 (5.0)
Banana juice/yogurt	99 (0.6)	92 (1.3)	90 (1.4)
Mixed fruit juice/yogurt	96 (5.1)	96 (5.1)	94 (1.3)
Grated apple with sugar and lemon	92 (2.0)	92 (3.1)	88 (0.9)
Smashed banana with sugar and lemon	100 (2.2)	98 (1.5)	91 (5.3)
Range of the Means	92-102	92-102	88-94

1. Batch No. P200550668 was used for production of 5,000 units USP lot No. P200550785 used for Study PR-001 study and EUR-1009-M.
2. A mean of 6 readings per batch.

Reviewer's Comments:

1. Based on the sponsor's data, applesauce and pear had the lowest pH (3.5-4.0) and vanilla pudding alone had the highest pH (5.5-6.1). However, the *in vitro* results presented in Table 4 did not show a correlation between food pH and lipase recovery. The testing procedures might have contributed to the variability.
2. The above in vitro study involved mixing capsule contents with food which was let stand for 60 minutes. However, we will instruct patients to take it immediately after mixing.

2. Detailed Labeling Recommendations

(b) (4)

(b) (4)

3. Appendices

3.1 Proposed Package Insert (02/05/09 version)

3.2 Study Synopsis (Addendum)

NDA 22-210 for Zenpep (Pancrelipase) MT Delay-Release Capsules

Appendix 1

Proposed Package Insert (02/05/09 Version)

NDA 22-210 for Zenpep (Pancrelipase) MT Delay-Release Capsules

Appendix 2

Revised Study Synopsis (01/09/09)

3 SYNOPSIS

Name of Sponsor: Eurand S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*For regulatory use only*
Name of Finished Medicinal Product: EUR-1008 (pancrelipase [Zentase™])	**Volume:**	
Name of Active Ingredient: Pancrelipase	**Page:**	
Title of Study:	Study of the Gastrointestinal Bioavailability of a Novel Pancreatic Extract Product (EUR-1008) in Chronic Pancreatitis Patients with Exocrine Pancreatic Insufficiency (Addendum)	
Investigator:	Phillip Toskes, MD	
Study Site:	Shands Hospital, University of Florida	
Publications:	None	
Period of Study:	Date of Study Initiation: 6 September 2007 Date of Study Completion: 17 July 2008	
Phase of Development:	1	
Objective(s):	Efficacy Objectives: The objective of the study was to determine the bioavailability of lipase, chymotrypsin, and amylase from EUR-1008 in the duodenum under fed conditions after administration of a test meal (Ensure Plus®) in patients with chronic pancreatitis (CP) with severe exocrine pancreatic insufficiency (EPI). The study also determined whether CCK blood levels were affected following the administration of EUR-1008. Safety Objectives: The safety objectives were to determine the frequency, duration, and severity of treatment-emergent adverse events (AEs) and changes in clinical laboratory findings.	
Methods:	This study was an open-label, randomized, single center, single treatment, 2-period, crossover trial. The study consisted of a screening period and a 5- to 6-day hospitalization period with 2 separate gastroduodenal	

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perfusion procedures.

Patients signed an informed consent before discontinuing any exclusionary drugs or undergoing any study procedures. Patients were allowed to sign the informed consent at home; they signed an additional informed consent at the time of hospitalization. Exclusionary drugs (proton pump inhibitors, antacids and drugs capable of altering gastrointestinal motility) were discontinued 7 days prior to entering the General Clinical Research Center (GCRC).

Day 1: After presenting their original signed informed consent and signing an additional informed consent on the day of hospitalization, patients entered the GCRC at the Shands Hospital, University of Florida. The Principal Investigator (PI) evaluated the eligibility of the patient for the trial, and medical history, physical examination, and blood and urine samples were collected.

Day 2: Patients were randomized to receive either a test meal (Ensure Plus) alone or Ensure Plus with EUR-1008, according to a predetermined randomization scheme. The dose of EUR-1008 was 75,000 USP lipase units (3 capsules containing 20,000 units each plus 3 capsules containing 5,000 units each) per procedure. After placement of the duodenal tube, perfusion and aspiration were begun, and duodenal washout and baseline samples were collected at 30 minutes and 60 minutes after the start of perfusion. At 60 minutes after the start of perfusion (after the baseline sample was collected), perfusion and aspiration were halted for 20 minutes to allow the patient to drink the test meal (Ensure Plus with or without EUR-1008). After this 20-minute meal break, perfusion resumed. Five minutes later, aspiration also resumed, and

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	both perfusion and aspiration were performed continuously for 2 hours. Samples were collected at 15-minute intervals for 2 hours. After 2 hours, aspiration of gastric contents was performed for 15 minutes (or for a maximum of 30 minutes if the sample quantity was insufficient). Day 3: Washout day. An abbreviated physical exam was done on this day. Day 4: The same procedures followed on Day 2 were repeated. Patients who received Ensure Plus alone on Day 2 received Ensure Plus with EUR-1008 on Day 4 or vice versa. Day 5: Complete physical exam and blood and urine samples were collected. Patients were discharged. The bioavailability of EUR-1008 was estimated by calculating the difference between the amount of lipase released and recovered in the duodenum (lipase output) under fed conditions with and without EUR-1008.	
Number of Patients (planned and analyzed):	12 evaluable male or female adult patients were planned and 17 patients were enrolled, 15 of whom were treated and had post-treatment data collected. Three patients were excluded from the Efficacy Analysis Population because of protocol violations (1 patient who did not meet inclusion/exclusion criteria, and 2 patients who were unable to tolerate the Dreiling tube and thus could not receive study medication). A fourth patient was excluded from efficacy analyses as a statistical outlier. The Efficacy Analysis Population therefore included 13 patients. The Safety Population included the 15 patients who received study medication.	

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Name of Active Ingredient: Pancrelipase	**Page:**	
Diagnosis and Main Criteria for Inclusion:	Patients of either sex over the age of 18 with a documented history of CP with severe EPI and significant steatorrhea and a fecal elastase level below 100 mcg/g.	
Test Product, Dose, and Mode of Administration, Batch Number:	EUR-1008 was administered orally with 480 mL of Ensure Plus as a single fixed dose of 75,000 USP lipase units (the contents of 3 capsules of 5,000 USP lipase units plus the contents of 3 capsules of 20,000 USP lipase units) per procedure per patient. Batch Number: 20,000 USP lipase units: 058761C; 5,000 USP lipase units: 058755B	
Duration of Treatment:	One administration of test product	
Reference Therapy, Dose and Mode of Administration, Batch Number:	480 mL Ensure Plus™ alone, orally	
Criteria for Evaluation:	The primary efficacy endpoint (the bioavailability of lipase from EUR-1008) was estimated by comparing the recovery of lipase under the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal. Secondary efficacy endpoints included the bioavailability of chymotrypsin and amylase estimated by comparing their recovery under the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal; the measurement of cholecystokinin (CCK) levels in blood; and the measurement of duodenal and gastric pH. Safety was evaluated in terms of the occurrence of adverse events (AEs) and changes in clinical laboratory parameters, physical examination findings, and vital sign	

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	measurements.	
Statistical Methods	Descriptive statistics of the various parameters and the corresponding lower and upper 95% confidence intervals (CI) were computed. For continuous variables, descriptive statistics for each treatment sequence included mean, standard deviation, median, lower and upper 95% CI, minimum, maximum, and number of non-missing observations. The descriptive statistics for dichotomous or categorical variables were numbers and percentages of each of the scores or categories for each treatment. The bioavailability of EUR-1008 was estimated by comparing the recovery of lipase, amylase, and chymotrypsin in the 2 treatment conditions (Ensure Plus alone and Ensure Plus with EUR-1008) after administration of the test meal. Statistical significance was evaluated by means of a paired samples t-test. Because 2 different pH subpopulations of patients were identified in this study, efficacy results and tabulations of data are also presented for a subpopulation (N = 11) of patients whose gastric pH was not excessively acid. Two patients whose pH values indicated acid hypersecretion were removed from this pH Subpopulation. All AEs were listed, and the frequency of treatment-emergent AEs was tabulated by system organ class and preferred term. All laboratory data were listed and analyzed using the appropriate statistical methods.	

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22210	ORIG 1		ZENTASE

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/s/

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08/12/2009

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08/17/2009