CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: July 21, 2009

To: Donna Griebel, M.D., Director
Division of Gastroenterology Products (DGP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)

Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Jessica M. Diaz, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): ZENPEP (pancrelipase)

Application Type/Number: NDA 22-210

Applicant/sponsor: Eurand Pharmaceuticals, Inc.

OSE RCM #: 2009-947

1 INTRODUCTION

This memorandum is in response to a request by the Division of Gastroenterology Products for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for ZENPEP (pancrelipase). Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. DRISK's review of the Medication Guide is being reviewed and will be provided under separate cover.

2 MATERIAL REVIEWED

- ZENPEP (pancrelipase) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated March 19, 2009
- Proposed ZENPEP (pancrelipase) Risk Evaluation and Mitigation Strategy (REMS), submitted in EDR on May 14, 2009

3 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to Eurand Pharmaceuticals, Inc:

See the appended ZENPEP (pancrelipase) REMS proposal (Appendix A) for track changes corresponding to comments in this review.

a. GOAL(S)

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risk associated with the use of Zenpep.

b. The Medication Guide distribution procedure does not provide sufficient details to determine whether it is in accordance with 21 CFR 208.24. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

- A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
- A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

Some content and format in your submission in the section "Medication Guide" is more appropriate for a REMS Supporting Document. The format

and content of the REMS should be revised as indicated in the appended REMS.

c. We remind you of the requirement to comply with 21 CFR 208.24:

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
  "Dispense the enclosed Medication Guide to each patient." or
  "Dispense the accompanying Medication Guide to each patient."

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

- You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Please submit for review a detailed plan to evaluate patients' understanding about the safe use of Zenpep (pancrelipase). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS-Other." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Zenpep (pancrelipase). This should include, but not be limited to:
  - Sample size and confidence associated with that sample size
  - How the sample will be determined (selection criteria)
  - The expected number of patients to be surveyed
  - How the participants will be recruited
  - How and how often the surveys will be administered
  - Explain controls used to minimize bias
  - Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).

- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

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/s/

Jessica Diaz
7/21/2009 04:31:56 PM
LABELING REVIEWER

Jodi Duckhorn
7/21/2009 04:33:01 PM
DRUG SAFETY OFFICE REVIEWER

Mary Willy
7/22/2009 11:19:41 AM
DRUG SAFETY OFFICE REVIEWER
SIgnoff as Acting Director DRISK

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 17, 2009
To:	Donna Griebel, MD, Director **Division of Gastrointestinal Products**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Robin Duer, RN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Medication Guide
Drug Name(s):	ZENPEP (pancrelipase) Delayed Release Capsules
Application Type/Number:	NDA 22-210
Applicant/sponsor:	Eurand Pharmaceuticals, Inc.
OSE RCM #:	2009-947

1. INTRODUCTION

This review is written in response to a request by the Division of Gastrointestinal Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for ZENPEP (pancrelipase) Delayed Release Tablets. Please let us know if DGP would like a meeting to discuss this review or any of or changes prior to sending to the Applicant. DRISK's review of the proposed REMS will be provided to DGP under separate cover.

2. MATERIAL REVIEWED

- Draft ZENPEP (pancrelipase) Delayed Release Capsules Prescribing Information (PI) submitted March 20, 2009 and revised by the Review Division throughout the current review cycle.

- Draft ZENPEP (pancrelipase) Delayed Release Capsules Medication Guide (MG) submitted on June 3, 2009.

3. DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 6.4, and a Flesch Reading Ease score of 68.8%. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The reading scores as submitted by the Applicant are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision*

Loss. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4. CONCLUSIONS AND RECOMMENDATIONS

1. We deleted the (b) (4) section as only information that is boxed or bolded in the PI is included in this section.
2. In the "What should I tell my doctor before taking ZENPEP?" section we deleted the information concerning (b) (4) The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. (b) (4)
3. In the "How should I take ZENPEP?" section we
    - revised two statements concerning crushing, chewing and swallowing ZENPEP Capsules. We bolded the "Do not crush" statement and moved it higher on the bulleted list to emphasize the Warnings and Precautions in the PI to "avoid irritation of oral mucosa".
    - separated the dosing instructions for infants and moved it to the end of this section for clarity. The instructions were expanded to include more specific, numbered steps for easier readability and understanding. Additionally, the PI states that contents of the ZENPEP capsules can be administered directly into the mouth of infants, so that was added. However, if the contents of the capsule are irritating to the mouth as the PI states, the RD should consider whether it would be safe to do that.
4. In the "What are the possible side effects of ZENPEP?" section
    - We added common adverse events as listed in the Warnings and Precautions section of the PI.
    - The Applicant's contact information is already included in the "General Information" section at the end of the PPI. To reduce redundancy, we encourage the Applicant to list their contact information in the "General Information" section only; however if the Applicant wants to include their phone number for reporting side effects in the "What are the possible side effects…" section too, they may do so. The additional language must be separated from the verbatim side-effects statement. We propose: "You may also report side effects to Eurand Pharmaceuticals, Inc. at 1-800-XXX-XXXX.

5. In the “General information about ZENPEP” section we added the information concerning pigs carrying viruses that could be transmitted to humans and deleted that information from the ‘ (b) (4) section. The Warnings and Precautions section of the PI mentions this information, so it was moved from the end of the MG to this section to emphasize its importance and relevance to ZENPEP.
6. We deleted the (b) (4) section as some of the information from this section was moved to a more appropriate section of the MG, and some of the information from this section was simply not appropriate for patient labeling.

Please let us know if you have any questions.

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/s/

Robin E Duer
7/17/2009 03:20:35 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/19/2009 08:24:32 PM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: **June 15, 2009**

To: **Elizabeth Ford, Regulatory Project Manager,**
Division of Gastroenterology Products (DGP)

From: **Shefali Doshi, Regulatory Review Officer**
Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: **Robert Dean, DTC Group Leader, DDMAC**
Lisa Hubbard, Acting Professional Group Leader, DDMAC
Jodi Duckhorn, Lead Social Science Analyst, OSE

Subject: NDA 22-210
DDMAC labeling comments for ZENPEP (pancrelipase) Delayed Release Capsules

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DDMAC has reviewed the proposed product labeling (PI), Carton and Container Labeling, and Medication Guide for ZENPEP (pancrelipase) Delayed Release Capsules (Zenpep) and offers the following comments.

The version of the draft PI used in this review is titled, "5-29 Zenpep response compared to 5-22 FDA version post labeling mtg 6-2.doc," accessed via the DGP eRoom on June 11, 2009. This document was last modified on June 10, 2009.

The version of the draft Carton and Container Labeling used in this review can be found at: \\FDSWA150\NONECTD\N22210\N_000\2009-06-04

The version of the draft Medication Guide used in this review can be found at: \\FDSWA150\NONECTD\N22210\N 000\2009-06-03.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PI or Carton and Container labeling, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

If you have any questions on the comments for the Medication Guide, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

PI

Highlights

General Comments

Please ensure that the content of the Highlights section is revised to be consistent with the content of the Full PI. For example, we note that chronic pancreatitis is referred to in the Highlights section, but is omitted from the Full PI.

Dosage and Administration

This section states, [redacted] (b) (4) Is this text essential? DDMAC notes that similar text does not appear in the labeling for Creon.

Full PI

General Comments

DDMAC notes that the proposed PI for Zenpep includes the abbreviations "EPI," "CF" and "PEP". We note that "EPI" and "CF" are defined in section 14; however, for clarity, please consider defining these abbreviations at first use.

1. Indications and Usage

This section states, "ZENPEP (pancrelipase) Delayed-Release Capsules is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis **or other conditions**" (emphasis added). [redacted] (b) (4)

2. Dosage and Administration

Section 2.2 states, [redacted] (b) (4)

5. Warnings and Precautions

Section 5.1 states, [redacted] (b) (4)

[redacted]

Section 5.2 states, [redacted] This text appears to be an incomplete sentence. Please consider revising the presentation.

Section 5.2 also states [redacted] Please consider revising to make both sections consistent.

6. Adverse Reactions

Section 6.1 states, "The incidence of adverse events (regardless of causality) [redacted] during double blind ZENPEP treatment [redacted] patients, 56%) and placebo treatment [redacted] patients, 50%)" (emphasis added). The bolded text appears promotional and may be used to minimize risks within a promotional context. Please consider revising, by stating directly the objective information, or deleting this sentence. We note that similar text also appears later in this section and in section 8.4.

Section 6.2 states, "In general, pancreatic enzyme products have a well defined and favorable risk-benefit profile in exocrine pancreatic insufficiency." This phrase appears promotional in tone and may be used to minimize risks within a promotional context. Please consider revising or eliminating this phrase.

8. Use in Specific Populations

Section 8.4 states, "When patient regimen was switched from their usual PEP regiment to ZENPEP at similar doses, patients showed [redacted]" (emphasis added). [redacted] Is there substantial evidence to support such claims? If not, please consider revising this text.

14. Clinical Studies

This section includes the following statements:

- [redacted]

(b) (4)

- (b) (4)
- (b) (4)

(b) (4) Is there substantial evidence to support such claims? If not, please consider revising this text.

16. How Supplied/Storage and Handling

This section states (b) (4) and are available in amber glass bottles (b) (4) (b) (4) If not, please consider deletion. We note that similar text does not appear in the labeling for Creon.

Carton and Container Labels

DDMAC has reviewed the proposed Carton and Container labels and has no comments. Reference is made to the review and comments by Kimberly Raines, Pharm.D.

Medication Guide

1. **"What is the most important information I should know about ZENPEP?"**

   A. The proposed Medication Guide states (b) (4)

   (b) (4)

2. **"What is ZENPEP?"**

A. The proposed Medication Guide states [redacted]

*According to the Indications and Usage section of the ZENPEP PI, "ZENPEP (pancrelipase) Delayed-Release Capsules is indicated for the treatment of **exocrine pancreatic insufficiency due to cystic fibrosis or other conditions**" (emphasis added). We note that the Highlights section of the PI also includes the condition of chronic pancreatitis.*

The indication statement in the proposed Medication Guide is too vague and it may broaden the indication of ZENPEP [redacted]

B. The proposed Medication Guide states (emphasis added):

[redacted]

The phrase [redacted] *We recommend deleting this phrase.*

We suggest that the statement "ZENPEP [redacted] *…." be revised to use language similar to what is in the CREON Medication Guide (i.e., "ZENPEP **contains** a mixture of digestive enzymes including lipases, proteases, and amylases"). We also suggest conveying the types of enzymes that are found in this product, as conveyed in the CREON Medication Guide.*

3. "What do I tell the doctor before I take ZENPEP?"

A. The proposed Medication Guide states "**Also tell your doctor if you**….are allergic to pork (pig products). The proteins in ZENPEP come from pork" (underline emphasis added).

We suggest that the underlined term be replaced with "pig."

B. The proposed Medication Guide states "**Tell your doctor about all the medicines you take**, including [redacted]

(b) (4)

We recommend that prescription medicines be included in the above list.

C. The proposed Medication Guide states (b) (4)

(b) (4)

4. **"How do I take ZENPEP?"**

A. *We recommend revising this section to clearly convey the dosage and administration instructions for infants up to 12 months of age and children and adults.*

B. *We recommend including, in consumer-friendly language, the reason why ZENPEP Capsules should not be crushed or chewed, mixed in foods with a particular pH, and why it should be followed with water or juice (if emptying the contents of the capsule onto food), as conveyed in the Dosage and Administration, Warnings and Precautions, and Patient Counseling Information sections of the ZENPEP PI (i.e., these actions can disrupt the protective enteric coating resulting in early release of enzymes, irritation of oral mucosa, and/or loss of enzyme activity).*

C. *Given the importance of the pH range of the foods that the content of the capsules should be added to, we feel that patients should be provided with examples of such foods (in addition to applesauce), as conveyed in the Dosage and Administration section of the ZENPEP PI.*

D. The proposed Medication Guide states the following regarding dosage and administration instructions for infants up to 12 months of age, (b) (4)

(b) (4)

*According to the Dosage and Administration section of the ZENPEP PI, "Contents of the capsule may be administered **directly to the mouth** or with a small amount of applesauce or other acidic food" (emphasis added). We recommend including that the contents can also be administered directly to the mouth.*

5. **"What are the possible side effects of ZENPEP?"**

A. The proposed Medication Guide states '(b) (4)

This section of the proposed Medication Guide omits the most common adverse events of contusion, cough, early satiety, and decreased weight, which are listed in the Highlights section of the ZENPEP PI. We recommend that the most common adverse events that are listed in the proposed Medication Guide be consistent with those listed in the Highlights section of the ZENPEP PI.

6. "What is in ZENPEP?"

A. *Should this section also convey what is in the imprinting ink and the shells of the capsules?*

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/s/

Shefali Doshi
6/15/2009 09:49:15 AM
DDMAC CONSUMER REVIEWER

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: NDA 22-210

Name of Drug: Zenpep® (Pancrelipase Capsules)

Sponsor: Eurand Pharmaceuticals Inc.

Material Reviewed: Zenpep® (Pancrelipase Capsules) Carton and Container Labels

OBP Receipt Date: February 4, 2009

Amendment Reviewed:

Background:

Zenpep® (Pancrelipase Capsules) is a New Drug Application (NDA) indicated as replacement therapy in patients with exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. Zenpep is a pancreatic enzyme product (PEP) consisting of porcine- derived lipase, protease, and amylase.

Labels Reviewed:

Zenpep® (Pancrelipase Capsules) Container Label

5,000 Lipase Units -12 ct and 100ct Sample Bottle; 100 ct and 500ct Trade Bottle
10,000 Lipase Units -12 ct and 100ct Sample Bottle; 100 ct and 500ct Trade Bottle
15,000 Lipase Units -12 ct and 100ct Sample Bottle; 100 ct and 500ct Trade Bottle
20,000 Lipase Units -12 ct and 100ct Sample Bottle; 100 ct and 500ct Trade Bottle

Zenpep® (Pancrelipase Capsules) Carton Label

5,000 Lipase Units -12 ct and 100ct Sample; 100 ct and 500ct Trade
10,000 Lipase Units -12 ct and 100ct Sample; 100 ct and 500ct Trade
15,000 Lipase Units -12 ct and 100ct Sample; 100 ct and 500ct Trade
20,000 Lipase Units -12 ct and 100ct Sample; 100 ct and 500ct Trade

Review

The carton and container labels for Zenpep® (Pancrelipase capsules) were reviewed and found to be adequate under most of the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
   Manufactured By: Eurand S.p.A., Pessano, Italy
   Marketed By: Eurand Pharmaceuticals, Inc. Yardley, PA 19067
   The mailing code is not included. This does not conform to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 42865--XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-On the left of the label "See package insert for dosage information." appears on all labels. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name with associated strengths- Zenpep® 5000, Zenpep® 10,000, Zenpep® 15,000, and Zenpep® 20,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Capsules. This does not conform to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase Capsules is used in type at least half as large as the most prominent presentation of the proprietary name, Zenpep®. This conforms to the regulation. Per United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, Monograph-Pancrelipase Delayed Release Capsules, the labeling should include Lipase, Amylase, and Protease activities in USP units. All of the ingredients are not listed. This does not conform to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements-

All required statements ("Rx Only" and "Protect from Moisture"). Protect from Moisture and does not appear on the label. The statement "Do not refrigerate" is not in bold. This does not conform to the regulation.

7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the right side of the label. This conforms to the regulation.

8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are not listed with corresponding units per capsule per 21 CFR 201.10. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label does prominently state the net quantity of contents in terms of numerical count in units on the lower portion of the label, below the proprietary and established name. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage- The label states "Dosage and Administration: See package insert for dosage." The label does not state that dosing is based on lipase units. This does not conform to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", identifying lot number, storage conditions, "Store in tight containers," and reference to the package insert. "PROTECT FROM MOISTURE" is not present on the label. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This does not conform to regulation.

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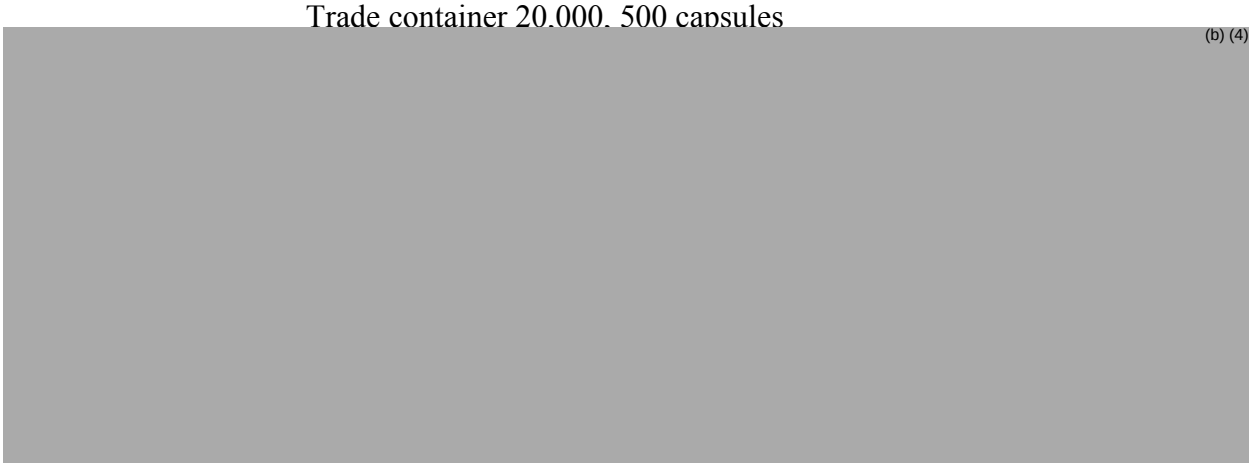
Trade container 20,000, 500 capsules

(b) (4)



II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
"Manufactured by: Eurand S.p.A. Pessano, Italy
Marketed by: Eurand Pharmaceuticals, Inc. Yardley, PA 19067."
The label requirement does not conform to the regulation

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers - The National Drug Code (NDC) number is located in the top 1/3 of the label in the right corner. It is noted as NDC 42865-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use - On the side panel in the lower half of the carton the statement "Dose and Administration: See package insert for dosage." appears. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name with associated strengths- Zenpep® 5000, Zenpep® 10,000, Zenpep® 15,000, Zenpep® 20,000 appears on the label. The established name, Pancrelipase appears as Pancrelipase Capsules. This does not conform to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients - The established name, Pancrelipase Capsules is used in type at least half as large as the most prominent presentation of the proprietary name, Zenpep®. This conforms to the regulation. Per United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, Monograph-Pancrelipase Delayed Release Capsules, the labeling should include Lipase, Amylase, and Protease activities in USP units. All of the ingredients are not listed. This does not conform to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements - All required statements ("Rx Only" and "PROTECT FROM MOISTURE") do not appear. "Do not Refrigerate" is not in bold font. This does not conform to the regulation.

7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date does appear on the carton under the lot number. This conforms to the regulation.

8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are not listed with corresponding units per capsule per 21 CFR 201.10. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents - The label does state the net quantity of contents in terms of numerical count in units on the bottom of the carton. This conforms to the regulation. Suggest increasing the font size.

11. 21 CFR 201.55 Statement of dosage - The label states "Dosage and Administration: See package insert for dosage." The label does not state that dosing is based on lipase units. This does not conform to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for "Rx Only", identifying lot number, storage conditions, "Store in tight containers," and reference to the package insert. "PROTECT FROM MOISTURE" is not present on the label. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This does not conform to regulation.

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III. Conclusions

A. The proposed carton and vial labeling are acceptable only upon the following changes:

1. Per 21 CFR 201.1(h) (6) (i), please include the applicable mailing code with the manufacturer information on the carton and container labels.

2. Per 21 CFR 201.6, Please revise the proprietary name to Zenpep® without associated strengths and the established name to Pancrelipase.

3. Per 21 CFR 201.10, 21 CFR 201.50, and the United States Pharmacopoeia, 5/1/09-8/1/09, USP 32/NF 27, Monograph-Pancrelipase Delayed Release Capsules, the labeling should include Lipase, Amylase and Protease activities in USP units per capsule on carton and container labeling.

4. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, "Protect from moisture" and "Avoid excessive heat" to the storage conditions listed on all labeling. In addition, bold the statement, "Do not refrigerate" on all carton and container labeling.

5. Per 21 CFR 201.55 and United States Pharmacopoeia, 5/1/09-8/1/09, USP 32/NF 27, Monograph-Pancrelipase Delayed Release Capsules -Please add a statement to the carton and container labels to indicate that dosing is based on lipase units.

6. Please add the statement, "Dispense the enclosed Medication Guide to each patient" per 21 CFR 208.24 on all carton and container labeling.

7. Per the United States Pharmacopoeia, 5/1/09-8/1/09, USP 32/NF 27, General Chapter <1091> Labeling of Inactive Ingredients, Please alphabetize the inactive ingredient listing in the "Description" section of the Package Insert. In addition, alphabetize the inactive ingredient listing within each strength.

8. Please consider increasing the font size of the net quantity statements listed on the carton labels for improved readability.

9. Please revise the Package Insert section, "Storage and Handling…" to include the statement, "Avoid excessive heat, above 35°C."

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Emanuela Lacana, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

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/s/

Kimberly Rains
6/1/2009 12:22:02 PM
CSO

Emanuela Lacana
6/2/2009 01:46:36 PM
CHEMIST

Barry Cherney
6/5/2009 01:53:05 PM
CHEMIST

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 5, 2009
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Zenpep (Pancrelipase Delayed-Release Capsules, USP)
Application Type/Number:	NDA # 22-210
Applicant:	Eurand
OSE RCM #:	2008-1231

CONTENTS

1 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton, and insert labeling submitted as part of the January 13, 2009 submission. (Appendix A thru H; no image of insert labeling)

1.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Because Pancrelipase is currently marketed, DMEPA conducted a search of the Adverse Events Reporting System (AERS) database to determine if medication errors related to the use of this product have been reported. DMEPA previously performed an AERS search for Pancrelipase in OSE review # 2008-2000, dated March 19, 2009. For this review, DMEPA performed an updated AERS search on April, 15, 2009 for medication errors submitted for Pancrelipase since the aforementioned review using the following terms: Established Name "Pancrelipase", Verbatim Name "Pancrl%" and the MedDRA reactions, "Medication Errors" (HLGT) and "Pharmaceutical Product Complaint" (PT). The updated AERS search did not retrieve any additional cases of medications errors involving Pancrelipase.

2 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 2.1 (*Comments to the Division)* for discussion during the review team's label and labeling meetings. Section 2.2 (*Comments to the Applicant)* contain our recommendations for the container label and carton labeling. We request these recommendations in Section 2.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Nina Ton, OSE Regulatory Project manager, at 301-796-1648.

2.1 COMMENTS TO THE DIVISION

A. Revise the strengths throughout the insert labeling (Highlights and Full Prescribing) to clearly represent the amounts of lipase, protease and amylase in each capsule.

B. The lipase component should not be presented without the protease and amylase components. Revise accordingly throughout the labeling.

C. Include the following revisions in the Dosage and Administration sections (Highlights and Full Prescribing):

1. Revise the symbol "≤" to read "less than or equal to". The ">" and "<" symbols are listed on the Institute for Safe Medication Practices (ISMP) "List of Error-Prone Abbreviations, Symbols, and Dose Designations". Additionally, in June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error prone abbreviations in prescribing. As part of this campaign, FDA agreed not to approve such abbreviations in their labeling.

2. Include the bolded statement "Zenpep capsules and capsule contents should not be crushed or chewed" to follow the first sentence in the second paragraph that ends with "….. adequate amounts of liquid".

3. Include a prominent statement at the beginning of this section informing patients and healthcare practitioners that Zenpep is dosed based on lipase units.

D. Revise the current dosage form "capsule" to read: "Delayed-Release Capsules" as this is a more accurate and appropriate dosage form designation for this product. The ONDQA chemist stated Zenpep is enteric-coated so by definition they are delayed-release capsules.

E. In the Dosage and Administration Highlights section's first sentence, delete the phrase "of body weight" that follows "….is 1,000 lipase units/kg/meal…".

F. In the Full Prescribing Dosage and Administration section, delete the duplicative sentence that reads: (b) (4) (third sentence in the second paragraph). This information is already conveyed in the first and second sentences of this paragraph.

G. In the How Supplied/Storage and Handling section, delete the references to (b) (4) and (b) (4) as these terms may result in confusion regarding the finished dosage form for this product.

2.2 COMMENTS TO THE APPLICANT

2.2.1 Container Labels and Carton Labeling

A. Revise the current dosage form (b) (4) to read: "Delayed-Release Capsules". Zenpep is enteric-coated so by definition they are delayed-release capsules.

B. The strength of the lipase component should not be presented without the strengths of the protease and amylase components. Revise your labels and labeling so that the proprietary name, established name, ingredients and strengths appear as follows:

Zenpep

Pancrelipase Delayed-Release Capsules

Each capsule contains:	
Lipase	XXXX USP Units
Amylase	XXXX USP Units
Protease	XXXX USP Units

The "each capsule contains…" boxes will represent the product strength on the principle display panel. Thus, the boxes (strengths) will need to be prominently displayed and distinctly distinguishable from one another. Differentiation may be accomplished through the use of colors, shading, highlighting or some other means. Based on postmarketing experience, labels and labeling that and are not adequately differentiated increase the risk of confusion and also contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered.

C. Include a statement on the principle display panel informing patients and healthcare practitioners that Zenpep is dosed based on lipase units.

D. Include the bolded statement: "Zenpep capsules and capsule contents should not be crushed or chewed" on the container labels and carton labeling.

E. Delete or decrease the size of the graphic which appears in front of the proprietary name. This will allow room to adequately present the strengths.

F. Include a statement alerting the dispenser to provide a Medication Guide for all strengths. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

1. "Dispense the enclosed Medication Guide to each patient." Or
2. "Dispense the accompanying Medication Guide to each patient."

G. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

1. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
2. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

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/s/

Deveonne Hamilton-Stokes
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DRUG SAFETY OFFICE REVIEWER

Todd Bridges
5/5/2009 11:33:57 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/5/2009 01:46:37 PM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 5, 2008

TO: Maureen Dewey, Regulatory Project Manager
Marjorie Dannis, Medical Officer
Division of Gastroenterology Products

FROM: Khairy Malek, M.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., MPH
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA : 22-210

APPLICANT: Eurand Pharmaceuticals, Inc.

DRUG: Zentase (pancrelipase USP) Capsules

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: 1. Treatment of exocrine pancreatic insufficiency

CONSULTATION REQUEST DATE: February 27, 2008 and May 7, 2008

DIVISION ACTION GOAL DATE: April 17, 2008 (extended to June 2008)

PDUFA DATE: June 17, 2008

I. BACKGROUND:

Exocrine pancreatic insufficiency (EPI) is a syndrome characterized by poor absorption of fats, proteins and to a lesser extent, carbohydrates. This manifests primarily in patients with cystic fibrosis and/or chronic pancreatitis. Treatment of EPI with pancreatic enzyme products has been well established for 3 decades, but most were developed before current FDA approval requirements. The FDA has requested manufacturers of PEPs (pancreatic enzyme products) to conduct efficacy and safety trials for these products.

The new NDA formulation, of enteric coated microspheres, provides better absorption of the enzymes. There is a safety concern that long term use of high doses may be associated with developing fibrosing colonopathy.

The review division selected two sites for inspection, Dr. Boas's site in IL and Dr. Schaeffer's site in FL. The two sites did not have the results of the fecal fat and nitrogen which were done at Mayo Central Laboratory in Rochester, MN. As a result, the field investigators could not verify the efficacy parameters. The review division agreed to extend the division action goal date so that DSI can inspect Mayo Laboratories and verify the study results.

II. RESULTS (by Site):

Name of CI Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Site 105 Steven Boas, M.D. Glenview, IL	Protocol # EUR-1008-M 6 subjects	04/25- 05/02/2008	VAI
Site 103 David Schaeffer, M.D. Jacksonville, FL	Protocol # EUR-1008-M 4 subjects	04/16- 04/17/2008	VAI
Mayo Central Laboratory for Clinical Trials Rochester, MN	Protocol # EUR-1008-M	05/30/2008	NAI (Pending)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Site 105: Steven Boas, M.D.
   2401 Ravine Way, Suite 302, Glenview IL 60025

   a. What was inspected: The field investigator reviewed the records of the 6 subjects in the study. There were no limitations to the inspection.

   b. General observations/commentary:

      Review of the subjects' records revealed a record maintenance violation. The CI did not have the actual results of the stool fat and nitrogen which were done at Mayo Central Laboratories in Rochester, MN. These results were sent directly from the lab to the sponsor.

   c. Assessment of data integrity: In order to verify the integrity of the data, DSI requested inspection of the Mayo lab. The Inspection showed that the results in the laboratory records were identical to those reported to the FDA.
      The data generated at this site are authentic and can be used in support of the NDA.

2. Site 103: David Schaeffer, M.D.
   807 Children's Way, Jacksonville, FL 32207

   a. What was inspected: The field investigator reviewed the records of the 4 subjects in the study. There was no limitation to the inspection.

   b. General observations/commentary: The CI did not have the results of the subjects' stool fat and nitrogen which were done at Mayo Central Laboratory.

   c. Assessment of data integrity: The field investigator could not verify the data sent by the sponsor. This required another inspection of the Mayo Central lab. Inspection of the lab showed that the data in the lab records were the same as what was reported to the FDA. The data generated at this site are authentic and can be used in support of the NDA.

3. Mayo Central Laboratory for Clinical Trials
   200 First Street, SW, Rochester, MN

   a. What was inspected: The field investigator compared the lab results of the above 2 sites (105 & 103) for the subjects fecal fat and nitrogen. There was no limitation to the inspection.

   b. General Observations: The field investigator compared the data from the lab records with the data reported to the FDA.

   c. Assessment of data integrity: Review of the data from Mayo Central Laboratory verified the integrity of the data reported by the sites 105 and 103.

The result of the Mayo Central Lab inspection was reported to me orally by the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

V. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The recommendation is that the data are reliable and can be used in support of the NDA.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., MPH
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Khairy Malek
6/5/2008 02:11:47 PM
MEDICAL OFFICER

Constance Lewin
6/5/2008 02:13:47 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 7, 2008
To:	Donna Griebel, M.D. Director, Division of Gastrointestinal Products
Thru:	Todd Bridges, RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Error Prevention
Subject:	Labeling Review for Zentase
Drug Name(s):	Zentase (Pancreatic Enzyme Product Delayed-Release Capsules) 5,000 USP Units , 10,000 USP Units , 15,000 USP Units, 20,000 USP Units
Application Type/Number:	NDA 22-210 (IND 70, 563)
Applicant/sponsor:	Eurand Pharmaceuticals Limited
OSE RCM #:	2008-436

CONTENTS

EXECUTIVE SUMMARY

The Division of Medication Error Prevention's analysis of the container label and carton labeling noted areas of vulnerability that could lead to medication errors. Improvements could be made to the labels and labeling to increase readability of information presented on the labeling. Such improvements include differentiating the product strengths from one another, increasing the prominence of the proprietary and established names, deleting the graphic which encircles these names, presenting the entire proprietary name in the same font color and without the period, relocating and presenting the product strength in its entirety with the accompanying unit of measure.

For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Gastrointestinal Products for a review of the container labels and carton labeling of Zentase. As previously communicated with the Project Manager during a Zentase meeting, we will defer insert labeling comments until after we have meet with the Division at the Zentase Labeling meeting. Therefore, our assessment of the insert labeling will be forthcoming under a separate review.

1.2 PRODUCT INFORMATION

Zentase is indicated in patients with (b) (4) . The recommended adult starting dose of Zentase is (b) (4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by our medication error staff to conduct a label, labeling and/or packaging risk assessment (see Section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on.

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. We use Failure Modes and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

For this product, the sponsor submitted on December 14, 2007, the following labels and labeling for our review (see Appendix A, B, C, D, E, F and G):

- (b) (4)

3 RESULTS

Container Labels and Carton Labeling (Trade and Professional Sample)

The graphic encircling the proprietary and established names is distracting.

The proprietary and established names appear small and lack prominence.

The proprietary name is presented in different colors. The letter 'Z' is presented in a fuchsia color whereas the remainder of the name is presented in the color purple.

There is a period at the bottom of the letter 'Z' in the proprietary name.

The net quantity is located near the product strengths.

The product strength is extremely prominent, does not immediately follow the established name and is separated by a graphic.

On the principle display panel of the container labels and carton labeling and the top panel of the carton labeling, the strengths have been truncated (e.g., 15 instead of 15,000) and do not contain a unit of measurement (i.e., USP Units). Additionally, these truncated strengths (5, 10, 15, and 20) are presented in the same font color.

The carton labeling contains a white rectangular box near the bottom.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

The product strength does not appear in conjunction with the trade name and the established name on the back panel of the carton labeling.

The NDC number appears in the bottom right corner of the carton labeling.

4 DISCUSSION

Our evaluation of the labels and labeling, noted several areas of needed improvement. The first area deals with the presentation of the proprietary and established names and the circular graphic that surrounds them. The presentation limits the size and prominence of the proprietary and established name because it must be contained within the circle graphic. Deleting the circle would allow the proprietary and established names to be increased in size allowing for greater prominence and increased visibility.

Additionally, the proprietary name appears in two different font colors. The first letter ('Z') of the proprietary name is fuchsia while the remaining letters in the name will be purple. The use of more than one color in the name of a drug product makes it more difficult to read. In addition, there should not be any symbols (e.g., a period) in the proprietary name, as this also decreases the readability of the name and may lead to misinterpretation of the name. Furthermore, in the current presentation, the fuchsia letter Z coupled with the period seem separate from the blue letters (entase). These factors can contribute to misidentification of the drug name.

The second area of needed improvement deals with the product strength. The strengths are extremely prominent and appear larger than the proprietary and established names. Although important, the strength should not be disproportionately larger than the proprietary and established names. The product strengths are also positioned flush right on the lower portion of the principle display panel and separated from the established name with intervening matter (e.g. circle graphic). This location is not the usual placement for strength. The usual presentation of information on the labels and labeling is: proprietary name, established name, and followed immediately by the product strength without any intervening matter. Practitioners are accustomed to this layout and when items appear in different locations and are separated by a graphic, it takes longer to locate and process the information.

We also noted that the strengths are truncated and do not include the unit of measurement. Not presenting the strength with a unit of measurement and not presenting the entire numerical strength is inaccurate, misleading and could lead to confusion. Furthermore, all of the strengths appear in the same fuchsia font color which increases the similar appearance of the labels. These bottles will be stored side-by-side on pharmacy shelves. Moreover, using the same colors increases the similarity of the numbers 5 and 15, which further increases the risk of confusion. Look-alike labels/labeling with similar color schemes may lead to product selection errors, especially when the products with these similar labels are stored in the same physical location. Also, the strength is located near the net quantity which increases the risk that the net quantity may be confused as the product strength, especially since the strength has no unit of measurement.

We also noted that the product strength does not appear with the proprietary name and established name on the back panel of the carton labeling. If the products are mistakenly shelved with the back panels facing out, the risk of selection error would be increased. In order to minimize the risk of selection errors, each presentation of the proprietary and established name should be accompanied in conjunction with the strength.

The third area of needed improvement surrounds the placement of the NDC number. The NDC number appears at the bottom one-third of the principle display panel. This placement is not in accordance with 21 CFR 207.35(b)(3)(i).

One other noted area of needed improvement involves the carton labeling which contains a white rectangular box near the bottom. It is not clear what this space will be used for. Although we assume this space is for prescription labels, we cannot be certain.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and layout design of the proposed container labels and carton labeling introduce vulnerability to confusion that could lead to medication errors with Zentase. The risks we have identified can be addressed and mitigated prior to approval. Recommendations are provided below in Section 5.2.

5.1 COMMENTS TO THE DIVISION

We have identified the following areas of needed improvement. We have provided recommendations in section 5.2 below and request that they be forwarded to the Applicant for implementation prior to approval of this application.

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any correspondence to the applicant pertaining to this issue. If you have further questions or need clarification, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Container Labels (Trade and Professional Sample)

1. Delete the circular logo surrounding the proprietary and established names as its inclusion decreases the size of the proprietary and established names.
2. Increase the size and prominence of the proprietary and established names. Additionally, ensure that the established name is at least ½ the size of the proprietary name and that the product strength is proportional in size and prominence to the proprietary and established names.
3. Present the proprietary name using only one color.
4. Remove the period/dot from the letter ‘Z’.
5. Revise the font color of the strengths to different color fonts to further differentiate the strengths.
6. Relocate the strength from flush right to immediately follow the established name without any intervening matter.
7. Present the product strengths in their entirety along with the units of measurement (e.g., 5,000 units, 10,000 units, 15,000 units and 20,000 units).

5.2.2 Carton Labeling (Trade and Professional Sample)

1. Delete the circular logo surrounding the proprietary and established names as its inclusion decreases the size of the proprietary and established names.
2. Increase the size and prominence of the proprietary and established names. Additionally, ensure that the established name is at least ½ the size of the proprietary name and that the product strength is proportional in size and prominence to the proprietary and established names.
3. Present the proprietary name using only one color.
4. Remove the period/dot from the letter 'Z'.
5. Revise the font color of the strengths to different color fonts to further differentiate the strengths.
6. Relocate the strength from flush right to immediately follow the established name without any intervening matter.
7. Present the product strengths in their entirety along with the units of measurement (e.g., 5,000 units, 10,000 units, 15,000 units and 20,000 units).
8. Include the product strengths on the back panels following the established name.
9. Please clarify the purpose of the large white rectangular box located near the bottom of the principle display panel.
10. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

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Deveonne Hamilton-Stokes
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DRUG SAFETY OFFICE REVIEWER

Deveonne Hamilton-Stokes
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DRUG SAFETY OFFICE REVIEWER

Todd Bridges
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/7/2008 02:18:31 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/7/2008 03:22:08 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERROR PREVENTION
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO22, Mailstop 4447)

DATE RECEIVED: March 28, 2007 **DATE OF DOCUMENT:** March 12, 2006	**DESIRED COMPLETION DATE:** August 1, 2007 **PDUFA DATE:** June 17, 2008	**OSE REVIEW #:** 2007-747

TO: Donna Griebel, MD
Director, Division of Gastrointestinal Products
HFD-180

THROUGH: Todd Bridges, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Deveonne Hamilton-Stokes, RN, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Zentase**
(Pancrelipase Delayed-Release Capsules, USP)
5,000 USP units, 10,000 USP units, 15,000 USP units and
20,000 USP units

NDA (IND)#: 22-210 **(**70,563)

SPONSOR: Eurand

RECOMMENDATIONS:

1. The Division of Medication Error Prevention does not recommend the use of the proprietary name, Zentase. We will proceed with an assessment of the alternate name, (b) (4) which will be forwarded in a separate review.

2. The Division of Medication Error Prevention's assessment of the container labels, carton and insert labeling will be forwarded in a separate review.

3. DDMAC finds the proprietary name, Zentase, acceptable from a promotional perspective.

We would be willing to meet with the Division for further discussion, if needed. We would appreciate feedback of the final outcome of this consult. Please copy us on any correspondence to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 22-210
Name of Drug: Zentase (pancrelipase) Delayed-Release Capsules
Applicant: Eurand Inc.

Material Reviewed:

Submission Date(s): December 14, 2007

Receipt Date(s): December 17, 2007

Submission Date of Structure Product Labeling (SPL): December 14, 2007

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

Labeling

The following issues have been identified in your proposed labeling.

Highlights Section:

- Avoid promotional or misleading terms [redacted] (b) (4)

Full Prescribing Information (FPI):

- Change the subheading to title case [redacted] (b) (4)

- Do not refer to adverse reactions as [redacted] (b) (4) [see Section 6.6]. Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance.

- Avoid using internal company study titles (e.g. EUR-1008-M).

- Correct the incorrect placement of a period (.) after Table 3.

- The manufacturer information should be located after the Patient Counseling Information section, at the end of the labeling (see 21 CFR 201.1 for drugs and 21 CFR 610).

Recommendations

Please address the identified issues and re-submit labeling by March 20, 2008. This updated version of labeling will be used for further labeling discussions.

Maureen Dewey, MPH
Regulatory Project Manager

Supervisory Comment/Concurrence:

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: MDD/February 26, 2008
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Maureen Dewey
2/28/2008 10:35:50 AM
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Julieann DuBeau
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