CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22210 SUPPL # HFD # 180

Trade Name Zenpep

Generic Name pancrelipase

Applicant Name Eurand Pharmaceuticals, Ltd.

Approval Date, If Known 8/27/2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

!

YES ☐ ! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES ☐ ! NO ☐

Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Elizabeth Ford
Title: Regulatory Health Project Manager
Date: 8-27-2009

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ELIZABETH A FORD
08/27/2009

DONNA J GRIEBEL
08/27/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-210 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Gastroenterology Products PDUFA Goal Date: 6/23/09 Stamp Date: 12/23/2009

Proprietary Name: Zenpep

Established/Generic Name: pancrelipase

Dosage Form: Delayed-release capsules

Applicant/Sponsor: Eurand Pharmaceuticals Limited

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Exocrine Pancreatic Insufficiency

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☒ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☒	Neonate	0 wk. __ mo.	4 wk. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☒ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☒ Other (e.g., patients geographically dispersed): patients are not usually diagnosed before 1 month.

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 1 mo.	__yr. 12 mo.	☐	☐	☒	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: Deferral requirement only for the development of 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.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	1 yr. __ mo.	16 yr. 11 mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☒ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__yr.___ mo.	___yr. ___mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

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

/s/

ELIZABETH A FORD
08/18/2009
This version of the PEDS page discussed with and approved by LMathis, RAddy, JBeitz, DGriebel, APariser, ARajpal

From: Nic Scalfarotto [nic.scalfarotto@eurand.com]
Sent: Wednesday, August 19, 2009 10:53 AM
To: Ford, Elizabeth
Subject: PMR Revision 8-19-09

Attachments: Post-marketing Commitments - 8-18-09 v 5.docx; emfalert.txt

Elizabeth,

Attached is the revised post-marketing requirements / commitments document inclusive of the changes that we discussed. The revised document will be sent to the document room today.

Regards,

Nic

Post-marketing Requirements
NDA 22-210 - Zenpep

1. **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.**

   Final report: December 31, 2010

2. **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

3. **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

Post-marketing Commitments
NDA 22-210 - Zenpep

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.**

   Final report submission: 9 / 2011.

2. **Develop and validate an infectious assay for PCV1.**

   Final report submission: 12 / 2010

3. **Establish lot release specifications for PCV1 for the drug substance.**

   Final report submission: 06 / 2011

4. **Establish lot release specifications for PPV and PCV2 for the drug substance.**

   Final report submission: 12 / 2009

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.**

   Final report submission: 06 / 2011

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.**

   Final report submission: 12 / 2010

7. **Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.**

   Final report submission: 12 / 2009

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.**

   Final report submission: 12 / 2009

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.**

   Final report submission: 12 / 2009

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

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

/s/

ELIZABETH A FORD
08/19/2009
PMR and PMC communication from applicant

From: Ford, Elizabeth
Sent: Monday, August 17, 2009 4:24 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22210/Zenpep/Post Marketing Commitments

Dear Dr. Scalfarotto,

Reference is made to NDA 22-210/Zenpep (pancrelipase) Delayed-Release Capsules. The Agency is requesting the following Post Marketing Commitments (numbered 4-12) :

4. Reevaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the manufacturing process. After **[insert number]** of drug product lots are manufactured, specifications will be reevaluated and adjusted to reflect manufacturing history and capability.

   Final Report Submission: by MM/YY

5. Develop and validate an infectious assay for PCV1.

   Final Report Submission: by MM/YY

6. Establish lot release specifications for PCV1 for the drug substance.

   Final Report Submission: by MM/YY

7. Establish lot release specifications for PPV and PCV2 for the drug substance.

   Final Report Submission: by MM/YY

8. 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.

   Final Report Submission: by MM/YY

9. 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.

   Final Report Submission: by MM/YY

10. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

    Final Report Submission: by MM/YY

11. 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.

    Final Report Submission: by MM/YY

12. 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 [insert date].

Note these are numbered sequentially to reflect that we have already communicated 3 post marketing *requirements*; as such, your first post marketing *commitment* is numbered '4'.

Thanks, and let me know if you have any questions.

Elizabeth

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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/s/

ELIZABETH A FORD
08/17/2009
Concurrence from Review Team: ELacana, HAnderson, ARajpal, JBeitz

From: Ford, Elizabeth
Sent: Monday, August 17, 2009 4:51 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22210/Zenpep/Package Insert

Attachments: Eurand Zenpep version 15 Aug 2009 marked with FDA comment.docx

Hello,

As per our conversation, please find attached the PI with FDA comment for your review. The Table of Contents section headings must be in bold type.

Please submit your revised PI as soon as possible.

Eurand Zenpep version 15 Aug 2...

Thanks,
Elizabeth

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

18 pp withheld in full immed. after this page as(b)(4) draft labeling.

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

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/s/

ELIZABETH A FORD
08/17/2009

From: Ford, Elizabeth
Sent: Friday, August 14, 2009 3:09 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22210/Zenpep/FDA comments to PI

Attachments: FDA version 14 Aug 2009.doc
Dear Nic,

Attached is the revised PI for NDA 22210 and FDA comments for your review.

Please let me know if you have questions.

Thanks,
Elizabeth

FDA version 14 Aug 2009.doc (2...

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

15 pp withheld in full immed. after this page as (b)(4) draft labeling.

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

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/s/

ELIZABETH A FORD
08/14/2009

From: Ford, Elizabeth
Sent: Friday, August 07, 2009 4:42 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22210/Zenpep/FDA comments/REMS and MEDGUIDE

Attachments: Zenpep Medication Guide FDA 8-7-09.doc; Zenpep REMS Revision - FDA 8-7-09.doc

Dear Nic,

FDA comments to the REMS and Medguide are attached to this email for your review. Please submit your revised REMS and Medguide as soon as possible. If you have any questions, I can be reached at the number provided below.

Thanks,
Elizabeth


Zenpep Medication Guide FDA 8...


Zenpep REMS Revision - FDA 8-...

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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

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/s/

ELIZABETH A FORD
08/07/2009

From: Nic Scalfarotto [nic.scalfarotto@eurand.com]
Sent: Tuesday, July 21, 2009 11:34 AM
To: Ford, Elizabeth
Subject: RE: NDA 22-210/Zenpep/Communication of PMRs

Dear Elizabeth,

I acknowledge receipt of your email detailing the requested post-marketing commitments.

Best regards,

Nic

Nic Scalfarotto, D.V.M.
Vice President Global Regulatory Affairs

Eurand Pharmaceuticals, Inc.
790 Township Line Rd. Suite 250
Yardley, PA 19067
Direct: 267.759.9357
Main: 267.759.9400
Mobile: 609.203.7290
Fax: 215.968.2941
www.eurand.com

From: Ford, Elizabeth [mailto:Elizabeth.Ford@fda.hhs.gov]
Sent: Tuesday, July 21, 2009 11:19 AM
To: Nic Scalfarotto
Cc: Ford, Elizabeth
Subject: NDA 22-210/Zenpep/Communication of PMRs

Dear Mr. Scalfarotto,

Reference is made to NDA 22-210/Zenpep (pancrelipase) Delayed-Release Capsules. Please be advised that Eurand will be responsible for the following Post Marketing Requirements:

1. 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.

2. 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.

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

For studies numbered 2 and 3, please submit, to your NDA, a timetable identifying the following milestone dates: **Final Protocol Submission Date, Study Completion Date, and the Final Report Submission Date**

At your convenience, please acknowledge receipt of this message.

Thanks,

Elizabeth Ford

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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/s/

ELIZABETH A FORD
08/04/2009

From: Ford, Elizabeth
Sent: Friday, July 24, 2009 3:24 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22-210/Zenpep/Communication of Comments for REMS

Follow Up Flag: Follow up
Flag Status: Red

Attachments: ZENPEP REMS DRISK Track changes.pdf

Dear Dr. Scalfarotto,

We are reviewing the REMS and Medguide submitted to NDA 22-210 and have the following comments and recommendations:

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 resubmit your revised REMS within 7-10 days.

ZENPEP REMS
RISK Track change.

Thanks,
Elizabeth

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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

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/s/

ELIZABETH A FORD
08/03/2009

From: Ford, Elizabeth
Sent: Friday, July 24, 2009 1:13 PM
To: 'Nic Scalfarotto'
Cc: Ford, Elizabeth
Subject: NDA 22-210/Zenpep/Medguide

Attachments: ZENPEP MG 7-24-09.docx
Hello,

The first round of revisions and comments to the Medguide have been completed for your review. Please review, and submit your revised medguide to NDA 22-210 in 7-10 days.

Thanks,
Elizabeth

ZENPEP MG
24-09.docx (30 KB)

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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

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/s/

ELIZABETH A FORD
08/03/2009

From: Ford, Elizabeth
Sent: Monday, August 03, 2009 5:12 PM
To: 'Nic Scalfarotto'
Subject: NDA 22210/Labeling/PI

Attachments: Zenpep Label to Applicant 8-3-09.doc
Hello,

Attached is the revised PI for NDA 22210 and FDA comments for your review.

Please let me know if you have questions.

Thanks,
Elizabeth

Zenpep Label to Applicant 8-3-...

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

15 pp withheld in full immed. after this page as (b)(4) draft labeling.

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

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/s/

ELIZABETH A FORD
08/03/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-210

GENERAL ADVICE

Eurand Pharmaceuticals, Ltd.
c/o Eurand Pharmaceuticals, Inc., U.S. Agent
Attention: Nic Scalfarotto, D.V.M.
Vice President: Global Regulatory Affairs
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Dr. Scalfarotto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed Release Capsules.

We also refer to your submissions dated April 30, 2008 and March 18, 2009.

We additionally refer to the Information Request (IR) letter we sent to you, dated March 2, 2009, in which we requested that you submit a partial pediatric waiver request (for patients aged less than 1 month), a pediatric deferral request (for studies in patients aged 1 month to less than 1 year), and an amended pediatric plan for NDA 22-210.

We have the following clarifications regarding the pediatric partial waiver, deferral, and plan requests:

1. We no longer require the previously submitted pediatric plan and pediatric deferral request to include patients aged 1 month to less than 1 year. After further consideration, the Agency intends to include in labeling for the pancreatic enzyme products (PEPs) as a class, dosing recommendations without restriction for children of all ages, with dosing guidelines per the Cystic Fibrosis Foundation (CFF). A recent evidence-based review of the published medical literature for the PEPs has reaffirmed these guidelines. In addition, evidence in the medical literature regarding the safety and effectiveness of the PEPs shows that children of all ages are expected to respond similarly to adults following treatment with PEPs. Thus, should your product be approved, the Agency has determined that it is appropriate to extrapolate both the efficacy and safety data from your pivotal trial in adults and older children (EUR-1008-M) to children as young as one month of age.

2. We continue to require the previously submitted partial waiver request for pediatric patients aged birth to less than 1 month.

3. For the pediatric studies that you have already conducted, should your product be approved, you will be able to include the safety and efficacy results from these pediatric studies in the labeling, which may appear in the Use in Specific Populations, Pediatric

Use (Section 8.4), Clinical Studies (Section 14), and Adverse Reactions (Section 6) sections of the labeling.

If you have any questions, call Elizabeth Ford, Regulatory Health Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
07/31/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210 **INFORMATION REQUEST LETTER**

Eurand Pharmaceuticals, Ltd.
c/o Eurand Pharmaceuticals, Inc., U.S. Agent
Attention: Nic Scalfarotto, D.V.M.
Vice President: Global Regulatory Affairs
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Scalfarotto:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed Release Capsules.

We are reviewing the Labeling section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The proposed carton and container labeling are acceptable only upon the following changes:

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

2. Per 21 CFR 201.6, revise the proprietary name to Zenpep® without associated strengths and the established name to (pancrelipase). The statement, "Delayed-Release Capsules" should appear in close proximity to the established name.

3. Per 21 CFR 201.15 and 21 CFR 201.100, 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.

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

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

6. Increase the font size of the net quantity statements listed on the carton labels for improved readability.

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

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

9. Delete or decrease the size of the graphic which appears in front of the proprietary name.

10. Delete the strength of the lipase component which appears to the right of the trade name as presenting the strength of only one of the ingredients is misleading.

11. As currently presented, the overlapping purple stripe used on the product strength to highlight each lipase component, along with the purple box outline, makes all of the strengths appear similar even though the background colors are different (see below). Differentiate the lipase component of each strength through some other means, rather than utilizing the same overlapping purple color bar. Additionally, revise the entire purple box outline color, which encompasses the "Dose by Lipase Units" and the product ingredients and strengths, to the color black.

If you have any questions, call Elizabeth Ford, Regulatory Health Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

7/8/2009 10:24:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

Eurand Pharmaceuticals, Limited
c/o Eurand Pharmaceuticals, Inc., U.S. Agent
Attention: William Gray, M.S.
Vice President, Regulatory Affairs
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed Release Capsules.

On June 15, 2009, we received your June 12, 2009 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 23, 2009.

If you have any questions, call Elizabeth Ford, Regulatory Health Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

6/17/2009 10:43:17 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ONDC

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2009

To: William Gray	**From:** Elizabeth Ford
Company: Eurand Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: 215-968-2941	**Fax number:**
Phone number: 267-759-9400	**Phone number:** 301-796-0193

Subject: FDA comments to draft labeling

Total no. of pages including cover:

Comments:

Document to be mailed: ☐ YES ☑ NO

From: Ford, Elizabeth
Sent: Friday, May 22, 2009 1:20 PM
To: 'William Gray'
Cc: Ford, Elizabeth
Subject: NDA 22-210/Zenpep/PI comments

Attachments: ZenpepPI FDA proposed 5-22-09.doc

Hello,

Please find attached to this message the suggestions for the package insert. Please respond as soon as possible, and let me know if you have any questions.

ZenpepPI FDA proposed 5-22-09...

Thanks,

Elizabeth

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

12 pp withheld in full immed. after this page as (b)(4) draft labeling.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

INFORMATION REQUEST LETTER

Eurand Pharmaceuticals, Limited
c/o Eurand Pharmaceuticals, Inc., U.S. Agent
Attention: William Gray, M.S.
Vice President, Regulatory Affairs
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed-Release Capsules.

We also refer to your submission dated May 7, 2009.

On April 23, 2009 we requested that you update your NDA by submitting all safety information regarding your drug. You responded by indicating (b) (4) and (b) (4) are responsible for safety reporting. You further indicated that "Eurand has no access to the safety database or any safety information from (b) (4)" and while you "have access to the safety data and product complaints from (b) (4), [you] have not received either since the time (b) (4) started distributing the unbranded pancrelipase product." Adverse Event forms for product complaints during the time (b) (4) marketed the unbranded pancrelipase product were submitted for review. This response is inadequate for the following reasons:

1. You have identified IND 70,563 and NDA 22-210 to support the continued marketing and enforcement discretion, as outlined in the Federal Register Notice dated October 26, 2007, Docket No. 2003N-0205, of your unbranded pancrelipase product. Therefore, you must submit the safety data for your unbranded pancrelipase product as requested in our April 23, 2009 letter to support the approval of Zenpep.

   In accordance with 21CFR 314.50(d)(5)(vi)(*a*) and (*b*), you are required to provide safety information that includes data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. Submit to the NDA a comprehensive summary of the worldwide experience on the safety of this drug.

   This comprehensive safety summary should include, but is not limited to, an updated estimate of the total exposure of the drug, including commercial marketing in the US and other countries, and from ongoing and completed clinical trials, and a comprehensive, integrated summary of the total safety experience of the drug, including overall side effect profile, any significant changes or findings in the safety profile from previous safety reports, any expedited safety reports, assessment of safety by subgroups (e.g., age, race, gender), and any other safety information learned about the drug that may reasonably affect the statement of contraindications, warnings,

precautions and adverse reactions in the draft labeling and Medication Guide for your drug. Also provide tabulations of the safety data, preferably as electronic datasets.

2. The proposed transition plan provided on May 7, 2009 was inadequate. Provide a proposed transition plan for the unbranded pancrelipase product to Zenpep in the U.S. marketplace. Include the following information in your transition plan:

    a. Describe, in detail, the period of time the two products will coexist on the marketplace. Provide a specific timeline, and include the schedule of events associated with the introduction of Zenpep and the withdrawal of the unbranded pancrelipase.

    b. Identify the steps to be taken to minimize transition time between the unbranded pancrelipase and Zenpep.

    c. Describe the anticipated activities planned to educate key stakeholders about Zenpep in order to prevent potential confusion with the unbranded pancrelipase.

In addition to the above requirements, the following information is requested:

3. Review the REMS/Medication guide that was issued with the Creon label; revise and resubmit your proposed REMS/Medication Guide.

4. For intubation study (PR001):

    a. Provide individual duodenal pH values at various times following administration of Ensure only (without Zenpep) for all patients in the original study. The data should be presented in the table format and as a plot (similar to the one submitted in the 1/9/09 submission).

    b. Provide similar information for all add-on patients for both Ensure only and Ensure + Zenpep as two separate tables and plots.

If you have any questions, call Elizabeth Ford, Regulatory Health Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

5/22/2009 11:46:41 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE/Nina Ton, OSE RPM	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Elizabeth Ford, RPM, DGP, 301-796-0193

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 4, 2009		22-210	REMS - MG	April 23, 2009 (earlies submission)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zenpep (pancrelipase)		pancreatic enzyme product	June 1, 2009

NAME OF FIRM: Eurand Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGP requests your expertise in the review of the medication guides and REMS documents submitted for Zenpep. Package inserts, MGs, and REMS documents have been provided under separate cover, and will additionally be available in the GI eRoom.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Elizabeth Ford	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Elizabeth A Ford
5/12/2009 11:28:19 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Wayne Amchin, DDMAC

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Elizabeth Ford, RPM, DGP, 301-796-0193

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 4, 2009		22-210	REMS - MG	April 23, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zenpep (pancrelipase)		pancreatic enzyme product	June 1, 2009

NAME OF FIRM: Eurand Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGP requests your expertise in the review of the medication guides and REMS documents submitted for Zenpep. Package inserts, MGs, and REMS documents have been provided under separate cover, and will additionally be available in the GI eRoom.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Elizabeth Ford	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Elizabeth A Ford
5/5/2009 05:13:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

INFORMATION REQUEST LETTER

Eurand Pharmaceuticals, Limited
c/o Eurand Pharmaceuticals, Inc., U.S. Agent
Attention: William Gray, M.S.
Vice President, Regulatory Affairs
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed-Release Capsules.

We also refer to your submission dated April 8, 2009.

In the original NDA submission, dated December 14, 2007, Zenpep is described by Eurand as "a novel formulation that has not been commercially available in any country and was designed to meet the United States (US) Food and Drug Administration (FDA) guidelines for PEPs." Through your recent correspondence, dated April 8, 2009, we have now become aware that Zenpep is a reformulation of Pancrelipase, the unbranded pancrelipase product (formerly known as Lipram) manufactured by Eurand. In consideration of this reformulation, we are reviewing the Clinical and Chemistry, Manufacturing and Controls (CMC) sections of your submission, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. On April 11, 2008 we requested that you update your NDA by submitting all safety information regarding your drug. In response, you submitted a Safety Update Report on May 20, 2008. This report indicated that the two active clinical studies (PR-001 and PR-002) constituted the "full worldwide human exposure of EUR-1008 during this reporting period." However, your April 8, 2009 correspondence indicated that "Eurand has continuously manufactured Pancrelipase since 1992." Given that Eurand has continuously manufactured the unbranded pancrelipase product since 1992, and in accordance with 21CFR 314.50(d)(5)(vi)(*a*) and (*b*), you are required to provide safety information that includes data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. Therefore, you must submit to the NDA a comprehensive summary of the worldwide experience on the safety of this drug.

   This comprehensive safety summary should include, but is not limited to, an updated estimate of the total exposure of the drug, including commercial marketing in the US and other countries, and from ongoing and completed clinical trials, and a comprehensive, integrated summary of the total safety experience of the drug, including overall side

effect profile, any significant changes or findings in the safety profile from previous safety reports, any expedited safety reports, assessment of safety by subgroups (e.g., age, race, gender), and any other safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling and Medication Guide for your drug. Also provide tabulations of the safety data, preferably as electronic datasets.

2. Submit CMC information for the unbranded pancrelipase product as follows:

    a. The name of the Drug Substance manufacturer, a summary of the manufacturing process, and DMF number.

    b. The name of the Drug Product manufacturer and a summary of the manufacturing process.

    c. A description of the formulation, and how it compares to the Zenpep formulation.

    d. A summary of studies conducted to evaluate the stability of the drug product.

3. Provide a proposed transition plan for the unbranded pancrelipase product to Zenpep in the U.S. marketplace. Include the following information in your transition plan:

    a. Describe in detail the period of time the two products will coexist on the marketplace. Include the schedule of events associated with the introduction of Zenpep and the withdrawal of the unbranded pancrelipase.

    b. Identify the steps to be taken to minimize transition time between the unbranded pancrelipase and Zenpep.

    c. Describe the anticipated activities planned to educate key stakeholders about Zenpep in order to prevent potential confusion with the unbranded pancrelipase.

If you have any questions, call Elizabeth Ford, Regulatory Health Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

4/23/2009 01:39:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

INFORMATION REQUEST LETTER

Eurand Pharmaceuticals, Inc.
Attention: William B. Gray
Vice President, Regulatory Affairs
US Agent for Eurand Pharmaceuticals
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your December 23, 2008 new drug application (NDA) resubmitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zenpep (pancrelipase) Delayed-Release Capsules.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Zenpep (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

Your proposed REMS must include the following:

> **Medication Guide**: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zenpep (pancrelipase) Delayed-Release Capsules poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zenpep (pancrelipase) Delayed Release Capsules. FDA has determined that Zenpep (pancrelipase) Delayed-Release Capsules is a product that is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. FDA has also determined that Zenpep (pancrelipase) Delayed-Release Capsules is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208,

you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zenpep (pancrelipase) Delayed-Release Capsules.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. 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.

In accordance with section 505-1, before we can continue our evaluation of NDA 22-210, you will need to submit the proposed REMS to this application. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Zenpep (pancrelipase) Delayed-Release Capsules. Once FDA finds the content acceptable, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for the assessments should include but may not be limited to:

a. Patients' understanding of the potential risks of Zenpep (pancrelipase) Delayed-Release Capsules.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission.

PROPOSED REMS FOR NDA 22-210

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-210 PROPOSED REMS-AMENDMENT

If you have any questions, please contact Elizabeth Ford, Regulatory Project Manager, at (301)796-0193.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Appendix A - REMS Template
Appendix B – REMS Supporting Document Template

Appendix A: Medication Guide REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. 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.

Appendix B: Medication Guide REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5. Include in section 3 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

TABLE OF CONTENTS

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/s/

Julie Beitz

3/19/2009 02:04:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

INFORMATION REQUEST LETTER

Eurand Pharmaceuticals Limited
Attention: William B. Gray, Vice President, Regulatory Affairs
US Agent for Eurand Pharmaceuticals Ltd.
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (pancrelipase) Delayed Release Capsules.

We also refer to your submission dated April 30, 2008.

We are reviewing the proposed pediatric plan in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please submit a partial pediatric waiver request for pediatric patients aged birth to less than 1 month.
2. Please amend your pediatric deferral to include pediatric patients aged 1 month to less than 1 year.
3. Please amend your pediatric plan to reflect the age group to be studied. The pediatric plan has to include a general description of the studies to be conducted and a timeline that includes the date you will submit the protocol, the date the studies will begin, and the date the studies will be submitted. The pediatric plan does not have to be a full protocol.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, RPh, M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin

3/2/2009 02:38:40 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
DGP/ODEIII HFD-180, Rm 5325

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/15/2009		22-210	NDA	10/27/2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zentase/Zenpep (pancrelipase)	Class 2 resubmission (6 month clock)	Pancreatic Enzyme	April 20, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: DDMAC: Please review the PI, carton and container labels (to be sent under separate cover to DDMAC reviewer).

PDUFA DATE: June 23, 2009
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-210
HFD-180/Division File
HFD-180/RPM
HFD-180/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Elizabeth Ford 301-796-0193	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Elizabeth A Ford

1/15/2009 04:44:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

Eurand Pharmaceuticals Limited
Attention: William B. Gray
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

We acknowledge receipt on December 23, 2008 of your December 22, 2008 resubmission to your new drug application for Zentase (pancrelipase) Delayed-Released Capsules.

We consider this a complete, class 2 response to our June 16, 2008 action letter. Therefore, the user fee goal date is June 23, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the review of this application has been completed, we will notify you whether we have deferred the pediatric study requirement for this application.

If you have any question, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, RN
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Elizabeth A Ford
1/13/2009 03:49:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

William B. Gray
Vice President, Regulatory Affairs
Eurand Pharmaceuticals Inc.
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

We acknowledge receipt on September 2, 2008 of your August 29, 2008 submission to your NDA 22-210 for Zentase.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiency from our action letter still needs to be addressed:

Chemistry, Manufacturing and Controls

5) The Nordmark DMF # 7090 has been reviewed in support of NDA # 22-210 and found to contain deficiencies. A letter has been sent to Nordmark listing the deficiencies. Nordmark should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify us when Nordmark has submitted the requested information.

If you have any questions, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey

9/18/2008 01:49:59 PM

	HFR-CE840DCB/ Warwick - release EIR per FMD-145 <u>CST send electronically to the following when in DFS</u> HFR-CE850/DIB/ Bigham HFR-CE850/BIMO/ Matson HFR-CE850/Field Investigator/ Matson HFR-CE840/DCB/ Warwick- release EIR per FMD-145 <u>CST send electronic copy to the following for a BLA:</u> <u>(BLAs are not in DARRTS or DFS) (Reviewer confirm)</u> Doc.Rm. BLA, or SBLA# Review Division Dir./last name Review Division/MO/ last name Review Division/PM/ last name DSI/Branch Chief/ last name DSI/GCP Reviewer/ last name DSI/GCP Branch CST/ last name DSI/Database PM/ last name GCF-1/Seth Ray HFR-xxx/DIB/last name HFR-xxx/BIMO/last name HFR-xxx/Field Investigator/last name HFR-xxx/DCB/last name, release EIR per FMD-145 HFC-134/Hackett/Kadar/Mercado (foreign letters only) <u>CST place paper copy in File:</u> DSI Doc. Rm. GCP File # 12611 <u>CST enter in Electronic Archive #</u> NDA # 22-210
Reviewer's Note to Review Division Medical Officer	This inspection was performed as a data audit PDUFA inspection for NDA 22-210. The review division requested inspection of 2 sites; Steven Boas, M.D. and David Schaeffer, M.D. At the 2 sites, the field investigators could not verify the integrity of the data reported to the FDA because the actual results of the stool fat and nitrogen were sent directly from the Mayo Central Laboratory to the sponsor. After consultation with the review division, DSI requested an inspection of the Mayo lab to assure that the efficacy data reported by the sponsor, are the same as those in the lab records. The inspection was done on 5/30/08 and the result was sent to you, based on verbal communication with the field investigator, to comply with the dates. The field investigator conducted an inspection of the Mayo laboratory and reviewed the lab results of all the subjects at the 2 sites. After reviewing the EIR, we find that the data reported are the same as those in the lab records. Khairy Malek MO

MEMORANDUM OF TELECON

DATE: 05/28/08

APPLICATION NUMBER: NDA 22-210

BETWEEN:

Name: William Gray, John Caminis, Massimo Latino, Giovanni Ortenzi, Luca Peloso

Representing: Eurand

AND

Name: Cristi Stark, Cherye Milburn, Donna Griebel, Joyce Korvick, Maureen Dewey, Anne Pariser, Dan Shames, Devonne Hamilton, Todd Bridges, Tien Mien Chen, Howard Anderson, Emanuela Lacana, Barry Cherney, Gibbes Johnson, Marjorie Dannis

SUBJECT: Discussion of Issues with NDA 22-210

On May 28, 2008, a teleconference was held with Eurand to discuss NDA 22-210 for Zentase for the treatment of pancreatic insufficiency. The purpose of this telecon was to brief Eurand on CMC issues still outstanding. FDA stated that all primary CMC reviews are complete and under supervisory review. FDA also added that the end of the review cycle is near and there are still a number of CMC items that are unresolved (including some items responded to by Eurand). The holders of the drug substance and the drug product Drug Master Files (DMF) will each receive a letter outlining deficiencies.

The call concluded.

_____

Cristi Stark, MS
Regulatory Health Project Manager

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/s/

Cristi Stark
6/2/2008 01:34:29 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

William Gray
Vice President, Regulatory Affairs
Eurand Pharmaceuticals Limited
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Mr. Gray:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

We also refer to your March 7, 2008, amendment, and have the following comments and requests for information:

1. In your original submission under Module 3, identical results (numbers) were found in the two tables shown below. For 11 types of food tested (except Applesauce Mott's), six dissolution readings per food type were all identical between two different small beads batches. Please verify the results or correct as necessary.

Table 3.2.P.2.2 - 48 Results of dissolution/ gastroresistance tests on small beads batch P200550387 after residence in food

1) Dissolution after (b) (4) (%)

Product	1	2	3	4	5	6	mean	C.V.
Applesauce Mott's	101	102	99	101	98	99	100	1.5
Applesauce Gerber	99	95	98	99	97	98	98	1.5
Bananas	100	98	99	98	99	97	99	1.1
Pears	97	102	99	100	98	100	99	1.8
Pudding Vanilla/ Apples	101	99	105	102	99	106	102	2.7
Banana pudding	99	103	102	99	104	105	102	2.5
Banana juice/ yogurt	98	100	99	99	99	99	99	0.6
Mixed fruit juice/ yogurt	97	98	99	86	95	89	96	5.1
Grated apple with sugar and lemon	92	94	93	94	89	92	92	2.0
Smashed banana with sugar and lemon	104	98	101	98	100	100	100	2.2

Table 3.2.P.2.2 - 49 Results of dissolution/ gastroresistance tests on small beads batch P200550648 after residence in food

1) Dissolution after (b) (4) (%)

Product	1	2	3	4	5	6	mean	C.V.
Applesauce Mott's	94	94	93	94	94	92	94	1.0
Applesauce Gerber	99	95	98	99	97	98	98	1.5
Bananas	100	98	99	98	99	97	99	1.1
Pears	97	102	99	100	98	100	99	1.8
Pudding Vanilla/ Apples	101	99	105	102	99	106	102	2.7
Banana pudding	99	103	102	99	104	105	102	2.5
Banana juice/ yogurt	98	100	99	99	99	99	99	0.6
Mixed fruit juice/ yogurt	97	98	99	86	95	89	96	5.1
Grated apple with sugar and lemon	92	94	93	94	89	92	92	2.0
Smashed banana with sugar and lemon	104	98	101	98	100	100	100	2.2

2. The above Table 3.2.P.2.2 (second table), included in your original NDA submission under Module 3, provided the dissolution results for batch P200550648, which is different from what you stated on page 94 of 100 (for batch P200550348), as follows:

Three batches of small beads manufactured for clinical/ stability purposes were tested, batches P200550387, P200550348 and P200550668, respectively used for the production of 5,000 U USP EUR-1008 batches P200550466, P200550756 and P200550785.

Please verify the accuracy of the batch numbers, and make corrections, if needed.

3. You indicated in your March 07, 2008 response to the Agency's February 15, 2008 information request comment #2 that the assay method used for lipase determination (b) (4) is similar to that for standard USP lipase assay method (using olive oil-gum Arabic emulsion).

Since the calculation of bioavailability (BA in %) involved the units reported by two different assay methods, please indicate the conversion factor for the lipase unit you used for the bioavailability (%) calculation and provide the supporting data. For example, one unit obtained by the (b) (4) is equivalent to X units by the USP method. Also, please provide a more detailed description on the calculation of bioavailability (BA %).

If you have already submitted the information as described above, please provide the location, and page and volume numbers in the submitted NDA.

4. Under section 10.5 for "Primary endpoints analysis" of your protocol PR-001, submitted in your appendices of Module 5 of your original submission, you state that "The bioavailability of EUR-1008 will be estimated from the amount of lipase released in the duodenum following administration of EUR-1008 in fed conditions (lipase output)". You also clarified in your March 07, 2008 response to the Agency's February 15, 2008 information request comment #3 that "At the end of the third hour, only the very last collection sample aspirates are drawn from the stomach".

   It appears that the individual dose recovered (Table 9 in Study report of PR-001, page 45/82, shown below) is the sum of lipase collected from duodenum (2^{nd} and 3^{rd} hour samples) and stomach (final gastric collection), if a non-zero value was obtained. For example, in patient #9, the reported dose recovered is 52,583 units (Zentase+Food Treatment group), which is the sum of 33,822 units (duodenal samples) and 18,761 units (gastric sample).

   Please calculate and provide in a separate dataset the information listed below for duodenal samples:

   1) The individual dose recovery (in units) from the duodenal samples "only" and its bioavailability (%), i.e., the fraction of administered dose of Zentase recovered in duodenum,
   2) The mean (SD) values of Dose Recovered and of Bioavailability (%) for PP population (n=8) and for Normal pH population (n=6), and
   3) p values.

   Please submit the above information in a separate table (similar to Table 9 below).

Table 9 - Lipase AUC and Dose Recovered by Treatment Group (Per Protocol and Normal pH Populations)

Patient No	Area Under Curve			Dose Recovered (units)		Bioavailability (%)
	Ensure Plus™ and EUR1008	Ensure Plus™ only	Difference	Ensure Plus™ and EUR1008	Ensure Plus™ only	
001	412200	222728	189472	27480	20041	10,82
002				1379	834	0,79
003	1510898	696060	814838	103193	51290	75,46
004	298418			20318	336	29,05
005	695273			55714	1507	78,81
006	379118			25785	4551	30,87
007		520770		0	37569	-54,62
009	648038	287280	360758	52583	19152	48,60
N = 8	Per protocol Population					
Total mean	657324 2	431709 5	455022 7	35806 5	16910 0	27 5
(SD)	(446410 75)	(217827 23)	(323164 09)	(34007 80)	(19074 07)	(43 31)
95% CI	188845-1125804	85098-778321	-347761-1257807	7375 - 64238	964 - 32856	-9 - 64
		p = 0 135		p = 0 116		
N = 6	Normal pH Population					
Total mean	657324 2	402022 7	455022 7	47512 2	16146 2	45 60
(SD)	(446410 75)	(256681 14)	(323164 09)	(31003 93)	(19276 97)	(27 22)
95% CI	188845-1125804	-235609-1039654	-347761-1257807	14976 - 80049	-4084 - 36376	17 - 74
		p = 0 135		p = 0 009		

5. Please provide your rationale for the adequacy of the bioavailability estimate based on study PR-001 where: 1) the collection of duodenal samples was only 2 hours; and 2) no balloon (or other blocking device) at the end of the Dreiling tube was used. In other words, please explain how you ensured that all lipase was recovered in the duodenal aspirates and no lipase passed through the duodenum.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Julieann DuBeau
5/19/2008 04:24:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
Eurand Inc.
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Dr. Caminis:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

We also refer to your amendment dated April 30, 2008 containing your proposed pediatric study protocol summary PR-004, and pediatric study deferral request for patients younger than one year of age.

We have reviewed your proposed pediatric study protocol summary PR-004 and have the following comments and recommendations:

1. You are proposing to include a total of four pediatric patients in the study. We recommend that you increase the total number of patients enrolled to at least six patients, and that that there be adequate representation of patients by age sub-groups (e.g., three patients each in the age sub-groups of 1 to 6 months and 6 to 12 months).

2. Since Zentase (EUR-1008) will be administered after capsules are opened and the drug product is mixed in applesauce or other soft foods, please revise the protocol to include safety assessments of the oral mucosa as part of the physical examination to look for any evidence of erosive changes or ulceration from exposure to the drug product.

3. You are proposing to allow for the administration of partial capsules of Zentase (EUR-1008), and that parents/caregivers estimate the dose to be given to patients by using a fraction of the beads contained in a capsule. We do not recommend that partial capsules be used, and that doses be estimated. Please ascertain that available capsule strengths (by lipase units) allow for sufficient flexibility to cover the expected dose range of product administration to meet the dosing requirements of the youngest, smallest patients.

4. Clarify the necessity for serial laboratory testing that will require multiple blood draws, such as hematology, chemistry, and liver enzymes, as part of the safety assessment for this very young patient population for a short-term study.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Donna Griebel

5/12/2008 08:13:00 AM

MEMORANDUM OF TELECON

DATE: April 8, 2008

APPLICATION NUMBER: NDA 22-210
Zentase (pancrelipase, USP) Delayed-Release Capsules

BETWEEN:

John Caminis, Vice President: Medical Affairs & Clinical Development
Massimo Latino, Zentase Team Manager

AND

FDA Attendees
Anne Pariser, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Reviewer
Virginia Elgin, M.D., Medical Reviewer
Maureen Dewey, M.P.H., Regulatory Project Manager

SUBJECT: Pediatric Deferral Request

On February 6, 2008, the Agency informed Eurand Pharmaceuticals that their application lacked a Pediatric Deferral Request (in children <1 year of age).

On February 12, 2008, Eurand Pharmaceuticals submitted their proposed pediatric plan which contained an explanation why they did not intend to study children <1 year of age.

During a teleconference on April 8, 2008, the Agency informed the sponsor that their application is required to contain an assessment of the safety and effectiveness of their product in pediatric patients <1 year of age unless this requirement is deferred. Dr. Pariser noted that the sponsor has not fulfilled the requirement.

Dr. Caminis stated that Eurand is planning on submitting a waiver for pediatric patients <1 year of age given the challenges of recruitment. Dr. Pariser acknowledged the difficulties of recruiting patients <1 year of age, but reiterated that under PREA requirements, a waiver is not likely to be granted. She recommended the sponsor request a deferral to study children <1 year of age.

Dr. Caminis acknowledged that Eurand will submit a deferral and inquired about the sample size requirements for these studies. Dr. Pariser noted that these studies should be able to demonstrate evidence of safety, could be similar in design to Study EUR-1009 (i.e., use spot fecal fat assessments for the effectiveness measure), and would only need to enroll a small number of

patients. Replicating the treatment cross-over design of EUR-1009 would be acceptable; however, the assessment of certain outcome measures, such as "abdominal pain", would not be appropriate in children <1 year of age. Mr. Latino inquired whether the data should be combined with the previous study results. Dr. Pariser emphasized the purpose of the studies is to demonstrate safety and may be performed with a small sample size without combining data from EUR-1009.

Dr. Caminis stated that they would confer with experts in Neonatology and likely submit the pediatric deferral request by May 1, 2008.

Maureen Dewey referred the sponsor to the Guidance for Industry "How to Comply with the Pediatric Research Equity Act1" and noted that the following items should be included as part of the Proposed Pediatric Plan:

1. A description of the planned studies in pediatric patients from 0 months < 1 year of age. This description should include a synopsis of the planned study protocol, which should contain information such as the study design (e.g., crossover, open-label), number of patients to be included in the study, length of treatment and endpoints to be assessed.

2. A projected date for the completion of the study and submission of the pediatric assessment.

Maureen Dewey requested feedback on the additional following information requests:

- Statistical SAS codes for primary efficacy analysis
- A desk copy of 3.2.P.5.1 containing information on the microbial limits test
- Two alternative trade names that do not contain modifiers (such as Zentase ^{EPI})

Eurand stated their agreement and promised to fulfill the requests by April 11, 2008.

The teleconference concluded at 11:48 AM.

_____

Maureen Dewey, M.P.H.
Regulatory Project Manager

1 Guidance for Industry "How to Comply with the Pediatric Research Equity Act" Draft, September 2005.

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/s/

Maureen Dewey

4/11/2008 09:36:25 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210 **INFORMATION REQUEST LETTER**

John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
Eurand Inc.
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Dr. Caminis:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

Please refer also to our April 8, 2008 telephone conversation regarding requirements for deferral of pediatric studies. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Pediatric Studies

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. Specifically, we note that pediatric patients less than one year of age were not included in your Clinical Development Program. Please submit the proposed Pediatric Plan for the assessment of safety and effectiveness of your product in pediatric patients less than one year of age, and include the following information in your proposed Pediatric Plan (for additional information, refer to the *Guidance for Industry*. How to Comply with the Pediatric Research Equity Act[1]):

1. A description of the planned study(ies) in pediatric patients less than one year of age. This description should include a synopsis of the planned study protocol, which should contain information such as the study design (e.g., crossover, open-label), number of patients to be included in the study, length of treatment, and endpoints to be assessed.

2. A projected date for the completion of the study and submission of the pediatric assessment.

[1] U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for Industry. How to Comply with the Pediatric Research Equity Act. Draft Guidance. September 2005. <http://www.fda.gov/cder/guidance/6215dft.pdf>.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Daniel A. Shames, M.D.
Division Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
4/11/2008 03:06:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

INFORMATION REQUEST LETTER

John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
Eurand Inc.
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Dr. Caminis:

Please refer to your December 14, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Statistics

Provide the SAS program code used for the primary and key secondary efficacy analyses for Study EUR-1008M titled, "a Randomized, Double-Blind, Placebo-Controlled Two-Treatment Cross-over Study to Evaluate the Safety and Efficacy of Eurand Pancreatic Enzyme Product (PEP) in Patients with Cystic Fibrosis and Exocrine Pancreatic Insufficiency". This program should access the data sets (.XPT files) already provided to the Agency in your submission dated February 12, 2008.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Julieann DuBeau
4/1/2008 02:52:32 PM

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.

DSI CONSULT: Request for Clinical Inspections

Date: February 27, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Consulting Review Division: Division of Gastroenterology Products/HFD-180
Marjorie Dannis, M.D., Primary Medical Reviewer
Anne Pariser, M.D., Medical Team Leader
Joyce Korvick, M.D., Deputy Director

From: Maureen Dewey, M.P.H., Regulatory Health Project Manager/Division of Gastroenterology Products/HFD-180

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-210
Sponsor/Sponsor contact information (to include phone/email): Eurand Pharmaceuticals Inc.
Drug: Zentase (pancrelipase, USP) capsule
NME: Yes
Standard or Priority: Priority
Study Population: Pediatric and Adults
Pediatric exclusivity: No

PDUFA Action Goal Date: June 17, 2008
Inspection Summary Goal Date: April 17, 2008

II. Background Information

This is a New Drug Application (NDA) for the new molecular entity, Zentase. Zentase is a pancrelipase enzyme product (PEP) intended for the treatment of exocrine pancreatic insufficiency (EPI) caused by cystic fibrosis, chronic pancreatitis, or other conditions (e.g., pancreatectomy).

Pancreatic Enzyme Products (PEPs) were first marketed prior to the Food Drug and Cosmetic Act of 1938 and continue to be available in the US as nutritional supplements and throughout the world as over-the-counter (OTC) and prescription therapies. In the 1990's there were concerns about the PEPs efficacy and safety Thus, a series of regulatory decisions were made which established that the PEPs were not generally recognized as safe and effective. The Agency then declared its intent to consider all PEPs as new drugs requiring an approved new drug application (NDA) for continued

marketing. At this time, there are no available PEPs marketed under a New Drug Application (NDA) approved by the FDA.

According to the sponsor, EUR-1008 is a new oral formulation which consists of hypromellose capsules of pancrelipase, formulated with enteric coated (EC) minitablets or EC microtablets. The EC microtablets are a special pediatric formulation designed to to be sprinkled on food. The active ingredient, pancrelipase, is a **concentrated porcine pancreatic extract** comprised of the pancreatic enzymes: lipase, amylase, and protease, as well as excipients in a compressed form.

III. **Protocol/Site Identification**

Site # (Name,Address, Phone number, email, fax#)	**Protocol #**	**Number of Subjects**	**Indication**
Site 105 Steven Boas MD Chicago CF care specialists 2401 ravine way suite 302 Glenview IL 60025	EUR-1008-M	6	treatment of exocrine pancreatic insufficiency
Site 103 David Schaeffer Nemours childrens clinic 807 childrens way Jacksonville fl 32207	EUR-1008-M	4	treatment of exocrine pancreatic insufficiency

IV. **Site Selection/Rationale**

Domestic Inspections:

Reasons for inspections (please check all that apply):

- x Enrollment of large numbers of study subjects (site 105)
- x High treatment responders (specify): site 103
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

International Inspections:
None requested

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Maureen Dewey at 301-796-0845.

Concurrence: (as needed)

Anne Pariser, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Reviewer

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/s/

Maureen Dewey
2/28/2008 08:51:51 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-210

Eurand Inc.
John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
790 Township Line Road, Suite 250
Yardley, PA 19067

Dear Dr. Caminis:

Please refer to your new drug application (NDA) dated December 14, 2007, received December 17, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zentase Delayed-Release Capsules (5,000, 10,000, 15,000, and 20,000 Units of Lipase).

We also refer to your submission dated February 12, 2008, which included the documents requested by the Agency on February 6, 2008.

We request that you submit the following information:

1. Product Quality Microbiology

Provide revised microbial limit specifications for drug product release and stability batches. Microbial limits specifications for non-aqueous preparations for oral use should comply with the USP <1111> recommended acceptance criterion of 10^2 CFU/g for total combined yeast and mold count.

2. Nonclinical Pharmacology:

Provide the maximum DAILY allowable levels in FDA approved products of the following inactive ingredients: hypromellose phthalate, triethyl citrate, and hypromellose.
Please justify the use of these excipients by published literature or by supporting toxicology studies if the estimated DAILY intakes of these ingredients from the pancrelipase formulation are higher than the maximum daily allowable levels present in the FDA approved products.

3. 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)] [see 21 CFR 201.57(c)(14)].

- 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).

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

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,
{See appended electronic signature page}
Daniel A. Shames, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Daniel A. Shames
2/28/2008 11:05:59 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

Eurand Inc.
John Caminis, M.D
Vice President, Medical Affairs and Clinical Development
790 Township Line Road
Suite 250
Yardley, PA 19067

Dear Dr. John Caminis,

We acknowledge receipt on February 15, 2008 of your February 15, 2008 correspondence notifying the Food and Drug Administration that the Regulatory representation and address has been changed from

Mehri Hezari-Adam, Ph.D.
Director, Regulatory Affairs
PPD, Inc.
1400 Perimeter Park
Morrisville, NC 27560

to

Dr. John Caminis, M.D
Vice President, Medical Affairs and Clinical Development
Eurand Inc.
790 Township Line Road; Suite 250
Yardley, PA 19067

for the following new drug application: NDA 22-210 for Zentase Delayed-Release Capsules.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey

2/25/2008 01:55:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Maureen Dewey, MPH
Regulatory Project Manager
DGP, ODE III, HFD-180 WO 22, RM 5159

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
01/11/2008	70,563	22-210	NDA	12/17/2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zentase or (b) (4) Delayed-Release Capsules	Priority	Pancretic Enzyme Product	May 12, 2008 60 Days prior to Action Date: March 30, 2008

NAME OF FIRM: Eurand

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the following proposed tradename for Zentase and/or (b) (4). A hard-copy of the label and carton have been sent directly to Todd Bridges. Please note that the Office of Regulatory Policy received a Citizen's Petition regarding the tradename Zentase. Please contact Nancy Boocker for more information. Please have a representative from OSE attend the team meetings scheduled for this application. First team meeting: February 27, 2008 1:00 pm.

PDUFA DATE: 06/17/2008
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-210
HFD-180/Division File
HFD-180/RPM

HFD-180/Reviewers and Team Leaders	
NAME AND PHONE NUMBER OF REQUESTER Maureen Dewey, M.P.H. (301) 796-0845	METHOD OF DELIVERY (Check one) ☒ DFS ONLY ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Maureen Dewey

2/25/2008 02:45:45 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
OPS/ONDQA/DPA II
Attn: Marie Kowblansky, Ph.D.
PAL
WO22 RM2466
10903 New Hampshire Avenue

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Maureen Dewey, MPH
Regulatory Project Manager
Division of Gastroenterology Products
WO 22 RM 5159
(301) 796-0845

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/20/2008		22-210	NDA	12/17/2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zentase	P	pancreatic enzyme replacement therapy	4/15/2008

NAME OF FIRM: Eurand

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☒ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
Please review the dissolution study of the drug product submitted in the NDA 22-210, received December 17, 2007. Please note this is a paper submission, volumes will be delivered to the appropriate reviewer. There is no DMF for this applicant.
PDUFA Goal date for NDA: 6/17/2008

SIGNATURE OF REQUESTOR
Wei Guo, Ph.D.
LCDR, US Public Health Service

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND

Review Chemist, HFD-122 FDA/CDER/OPS/OBP/DTP Room 2B24, Building 29A 8800 Rockville Pike Bethesda, MD 20892	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Maureen Dewey

2/20/2008 01:22:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-210

Eurand Inc.
John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
790 Township Line Road
Suite 250
Yardley, PA 19067

Dear Dr. Caminis:

Please refer to your new drug application (NDA) dated December 14, 2007, received December 17, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zentase.

We also refer to your submission dated February 12, 2008, which included the documents requested by the Agency on February 6, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 17, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application for pediatric patients one year of age or older. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, please call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Daniel A. Shames, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Daniel A. Shames
2/20/2008 03:14:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210 **INFORMATION REQUEST LETTER**

John Caminis, M.D.
Vice President, Medical Affairs and Clinical Development
Eurand Inc.
790 Township Line Road
Suite 250
Yardley, PA 19067

Dear Dr. John Caminis:

Please refer to your December 17, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical Pharmacology

1. Provide detailed information on sample handling of duodenal aspirates between their collection and sample preparation prior to assay, since the pH value and possible changes during the preparation processes are critical to the assay. If you have already submitted the needed information, please indicate the location of the information (volume and page numbers) in your NDA.

2. The above assay method is seemingly not specific for lipase determination. For example, the amount of gastric acid in the sample can affect the pH. Please explain how a method without specificity can be suitable for the desired purposes.

3. Report of pH in Tables 22 and 23 (p. 62-63 of 82) showed the pH values of combined gastric and duodenal samples. Since the evaluation of lipase activity available at site of action (duodenum) is the main purpose for this study, please report the pH values of gastric and duodenal samples separately in different tables. Also please clarify if the lipase activity in gastric and duodenal samples is analyzed and reported separately.

4. The in vitro stability of Zentase when mixed with food should be studied as stated in your proposed package insert "capsules (contents) can also be sprinkled on relatively acidic soft foods (i.e., commercially available preparations of banana, pears, and applesauce […]."

The foods allowed in the labeling should be supported by the stability data. The pH values of the foods should also be provided.

5. Indicate whether you submitted the in vitro stability study requested on April 26, 2007. If you have already submitted the requested information, please indicate the location of this information (volume and page numbers) in your NDA.

If you have any questions, call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff (CPMS)
Division of Gastroenterology Products
Office of Drug Evaluation III

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/s/

Julieann DuBeau
2/15/2008 12:28:38 PM

MEMORANDUM OF TELECON

DATE: February 6, 2008

APPLICATION NUMBER: NDA 22-210
Zentase (pancrelipase, USP) Delayed-Release Capsules

BETWEEN:

Gearoid Faherty, Chief Scientific Officer (*ad interim*)
Marco Sardina, Director Medical Affairs
Massimo Latino, Zentase Team Manager
Bruce Merchant, Regulatory/Clinical Consultant
Mark Lostrom, Regulatory/Clinical Consultant
Mehri Hezari-Adam, Director, Regulatory Affairs PPD/ US Agent for Eurand

AND

FDA Attendees
Daniel A. Shames, M.D., Division Director
Anne Pariser, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Reviewer
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer
Maria R. Walsh, R.N., M.S., Project Management Officer, ODE III
Sally Loewke, M.D., Associate Director of Policy, Office of New Drugs
Maureen Dewey, M.P.H., Regulatory Project Manager

SUBJECT: Filing Deficiencies

On February 6, 2008, the Agency notified Eurand Pharmaceuticals that their application, NDA 22-210, did not contain the following items:

- Integrated Summary of all available information about the safety of the drug product (ISS)
- Integrated Summary of all available information about the efficacy of the drug product (ISE)
- Define.pdf file for datasets (data definition)
- Pediatric Deferral Request (in children ≤ 1 year of age)

Mehri Hezari explained that Eurand performed two clinical studies, each in different patient populations, and therefore, the company did not believe they were required to integrate the data in an ISS or ISE.

Dr. Anne Pariser noted that the ISS and ISE are required components of an application, and are of particular importance for this submission as there is an extensive commercial-use safety and

efficacy history with Zentase (and other pancreatic enzyme products) that will need to be included in both the ISS and ISE. It is the expectation of the Division that the ISS and ISE will be comprehensive documents that thoroughly describe the product's safety and efficacy. Eurand was referred to the Agency's website for Guidance on the content and structure of the ISS and ISE (see www.fda.gov/cder/guidance/7621dft.pdf).

The Agency provided the sponsor with their regulatory options, including the opportunity to: submit the ISS and ISE prior to the filing date, February 15, 2008, or withdraw the submission dated December 14, 2007, which notified that Agency that this was the last piece of the rolling review, and resubmit the last piece with all required components. The Agency stated that they would not be able to file the application without the aforementioned components.

Eurand requested additional time to consider their options and would notify the Agency within one day of their decision. Eurand inquired whether the Agency would consider an extension of the filing date. The Agency stated that an extension to the filing date cannot be given.

Additionally, Dr. Chen communicated the following clinical pharmacology questions and comments to Eurand regarding the *in vivo* intubation Study PR-001:

1. Please provide detailed information on sample handling of duodenal aspirates between their collection and sample preparation prior to assay, since the pH value and possible changes during the preparation processes are critical to the assay.

2. The proposed assay method is seemingly not specific for lipase determination. For example, the amount of gastric acid in the sample can affect the pH. Please explain how a method without specificity can be suitable for the desired purposes.

3. Report of pH in Tables 22 and 23 (p. 62-63 of 82) showed the pH values of combined gastric and duodenal samples. Since the evaluation of lipase activity available at site of action (duodenum) is the main purpose for this study, please report the pH values of gastric and duodenal samples separately in different tables. Also please clarify if the lipase activity in gastric and duodenal samples is analyzed and reported separately.

4. The *in vitro* stability of Zentase mixed with food should be studied. Your proposed package insert states "capsules (contents) can also be sprinkled on relatively acidic soft foods (i.e., commercially available preparations of banana, pears, and applesauce, grated apple with sugar and lemon, smashed banana with sugar and lemon)..." The foods allowed in the labeling should be supported by the stability data, and the pH values of the foods should also be provided.

The Agency summarized that the following required components will be needed in order for the application to be considered complete:

- ISS,
- ISE,
- Define.pdf file for datasets, and

- Pediatric Deferral Request (in children ≤ 1 year of age).

Responses to the Clinical Pharmacology questions may be submitted as an amendment to the NDA at a later time.

Eurand stated their agreement and would communicate their decision to the Regulatory Project Manager within the next day.

The teleconference concluded at 1: 20 PM.

_____

Maureen Dewey, M.P.H.
Regulatory Project Manager

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/s/

Maureen Dewey
2/8/2008 10:32:56 AM

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

DATE: 2/5/08

TO: DFS File

FROM: Stephen E. Langille, Ph.D.

THROUGH: James McVey – Team Leader

cc: Maureen Dewey – Project Manager

SUBJECT: NDA 22-210

On December 14, 2007, Eurand Pharmaceuticals Limited submitted NDA 22-210 for Zentase (pancrelipase) pancreatic enzyme product. The drug product is a solid oral dosage form with a (b) (4) of no more than (b) (4) The applicant has proposed microbial limit specifications for the drug product of (b) (4) CFU/g of total bacteria and an absence of *E. coli* and *Salmonella* species. The applicant did not provide a specification for total yeast and mold count because the drug substance has a specification of no more than (b) (4) CFU/g for yeast and mold. However, this specification does not account for yeast and mold contamination of the finished drug product via the manufacturing process and/or excipients.

The following comment should be provided to the applicant:

1. Microbial limits specifications for non-aqueous preparations for oral use should comply with the USP <1111> recommended acceptance criterion of 10^2 CFU/g for total combined yeast and mold count. Please provide revised microbial limit specifications for drug product release and stability batches.

END

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/s/

Stephen Langille
2/8/2008 08:13:18 AM
MICROBIOLOGIST

James McVey
2/8/2008 11:28:50 AM
MICROBIOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-210

NDA ACKNOWLEDGMENT

Eurand Inc,
Attention: Bhanu Balasubramaniam, RAC
Regulatory Affairs Manager
Authorized US Agent for Eurand Pharmaceuticals Limited
845 Center Drive
Vandalia, OH 45377

Dear Ms. Balasubramaniam:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zentase (EUR-1008) Pancrelipase Capsules 5, 10, 15, 20

Date of Application: December 14, 2007

Date of Receipt: December 17, 2007

Our Reference Number: NDA 22-210

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products, HFD-180
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey

12/31/2007 11:27:17 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA PRESUBMISSION ACKNOWLEDGEMENT

NDA 22-210

EURAND, Inc.
Attention: Bhanu Balasubramaniam, RAC
Regulatory Affairs Manager, US Agent
845 Center Drive
Vandalia, OH 45377

Dear Ms. Balasubramaniam:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Zentase (5,000; 10,000; 15, 000; 20, 000 USP) Units of Lipase per capsule

Date of Submission: May 30, 2007

Date of Receipt: June 1, 2007

Our Reference Number: NDA 22-210

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey

6/7/2007 12:54:03 PM