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*APPLICATION NUMBER:*

**22-210**

**OTHER ACTION LETTER(s)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-210

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

Dear Mr. Gray:

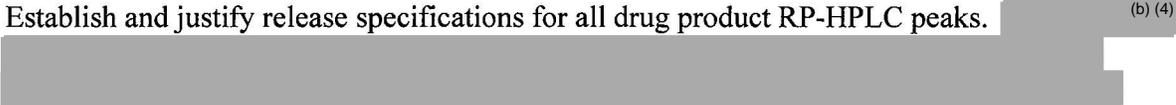
Please refer to your new drug application (NDA 22-210) dated December 14, 2007, received December 17, 2007, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zentase (EUR-1008) Pancrelipase Delayed-Release Capsules 5, 10, 15, 20.

We acknowledge receipt of your submissions dated February 7, February 12, February 15, March 7, March 11, March 20, March 22, March 27, March 31, April 14, April 18, April 30, May 20, June 6 and June 9, 2008.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

Chemistry, Manufacturing and Controls

- 1) In section 3.2.P.3.5 (Submission dated July 31, 2007, Vol. 2, Section 3.2.P.3.5, pg 1) you indicate that process validation to the intended full commercial batch size for each manufacturing step will be completed prior to marketing. Please provide a summary of the anticipated validation program. Process validation should be performed on three consecutive, commercial scale drug product conformance lots. Please indicate when validation studies will be initiated and completed.
- 2) Provide detailed information regarding the chemistry, manufacturing and controls for the hypromellose phthalate used for enteric coating of the beads/small beads.
- 3) The stability data contained in your application are insufficient to support your requested dating period of (b) (4) for the drug product. ICH Q5C indicates that expiry dating of products in which the active components are proteins should be set using real time, real temperature stability data. Therefore, the data provided support an 18-month expiry.
- 4) Specify how long excursions up to 30°C are permitted, and provide data to support the excursions.
- 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.

- 6) You have not submitted sufficient information in the NDA to evaluate your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.
- 7) In regard to specifications for release and stability, acceptance criteria should be established based on manufacturing history, process capability and clinical experience. We have the following recommendations:
  - a) Tighten acceptance criteria for the protease and amylase activity to reflect actual manufacturing capability, for both final and intermediate drug product.
  - b) Establish and justify release specifications for all drug product RP-HPLC peaks. (b) (4)  
  
Therefore, the current release specifications and stability specifications are not adequate.
  - c) Establish a release specification for Phthalic Acid (FPA) for the four drug product strengths, and provide a justification for the acceptance criteria chosen.
  - d) Revise the acceptance criteria for the Uniformity of Dosage Units so that they are the same for the clinical/stability lots and for the lots to be marketed. The proposed weight limit of (b) (4) of target fill weight is too broad to ensure consistent manufacturing of EUR-1008.
  - e) Establish and justify a specification for water content for drug product release and stability testing.
- 8) As part of the RP-HPLC assay validation, determine how much protein is retained on the column.
- 9) Develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured. The certificate of analysis for the RP-HPLC pancrelipase reference standard release testing only includes specifications for peak areas. We also recommend that an internal reference standard that reflects the commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing.
- 10) The working standard certificate of analysis for batch # P13309305 has two different USP lipase specific activities depending on the USP reference standard used. Please develop and implement a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the reference standard.

#### Clinical Pharmacology

- 11) In an Information Request letter sent on February 15, 2008, we requested clarification of the *in vitro* stability data you provided in the July 31, 2007, submission (Module 3, Section 3.2.P.2.2 Drug Product, pp. 91-100). In your submission, you evaluated the *in vitro* stability of pancrelipase after the capsules were opened and the contents were mixed with various types of food. You

provided the stability data for three batches of EUR-1008 capsules; however, we noted that the individual data for two of the three batches were identical. It is not clear to us whether these are the actual results, or whether there were errors in the dataset. Provide clarification on the stability data as part of your complete response.

### Inspection

Prior to approval, an acceptable inspection of your manufacturing facilities is required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

NDA 22-210

Page 4

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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.  
Deputy Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Daniel A. Shames  
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