DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022210 **NDA APPROVAL**

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) dated December 14, 2007, received December 17, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zenpep (pancrelipase) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated February 7, 2008, February 12, 2008, February 15, 2008, March 7, 2008, March 11, 2008, March 20, 2008, March 22, 2008, March 27, 2008, March 31, 2008, April 14, 2008, April 18, 2008, April 30, 2008, May 20, 2008, June 6, 2008, June 9, 2008, December 22, 2008, January 9, 2009, January 22, 2009, February 5, 2009, March 16, 2009, March 20, 2009, April 8, 2009, April 23, 2009, May 7, 2009, May 14, 2009, May 18, 2009, June 3, 2009, June 4, 2009, June 8, 2009, June 12, 2009, June 17, 2009, June 22, 2009, June 30, 2009, July 10, 2009, July 17, 2009, July 27, 2009, August 3, 2009, August 4, 2009, August 10, 2009, August 12, 2009, August 14, 2009, and August 15, 2009, August 18, 2009, and August 19, 2009.

The December 22, 2008 submission constituted a complete response to our June 16, 2008 action letter.

This new drug application provides for the use of Zenpep (pancrelipase) Delayed-Release Capsules for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

We have completed our review of this application, as amended. It is approved effective the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt,

we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022210**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, submitted on August 18, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).*

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022210**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed before the age of 1 month, so there would not be enough eligible patients in this age range to study.

We note that you have fulfilled the pediatric study requirement for ages 1 year to 17 years for this application. The pediatric requirement for 1 month to 1 year is not fulfilled due to the lack of an age appropriate formulation.

We are deferring submission of an age appropriate formulation. The status must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This requirement is listed below.

1521-1. Deferred requirement for development of an age appropriate formulation for Zenpep (pancrelipase) Delayed-Release Capsules: 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.

Submit final reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing requirement must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

1521-2. 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.

The timetable you submitted on August 19, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission: July 15, 2010
Study Completion Date: July 1, 2022
Final Report Submission: December 31, 2022

1521-3. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Zenpep (pancrelipase) Delayed-Release Capsules.

The timetable you submitted on August 19, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission: July 15, 2010
Study Completion Date: July 1, 2022
Final Report Submission: December 31, 2022

Submit the protocols to your IND 070563, with a cross-reference letter to this NDA 022210. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We remind you of your postmarketing study commitments in your submission dated August 19, 2009. These commitments are listed below.

1521-4. Re-evaluate 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 re-evaluated and adjusted to reflect manufacturing history and capability.

Final Report Submission: by September 2011

1521-5. Develop and validate an infectious assay for PCV1.

Final Report Submission: by December 2010

1521-6. Establish lot release specifications for PCV1 for the drug substance.

Final Report Submission: by June 2011

1521-7. Establish lot release specifications for PPV and PCV2 for the drug substance.

Final Report Submission: by December 2009

1521-8. 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 June 2011

1521-9. 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 December 2010

1521-10. 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 December 2009

1521-11. 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 December 2009

1521-12. 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 December 2009.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**

- **POSTMARKETING COMMITMENT - FINAL REPORT**
- **POSTMARKETING CORRESPONDENCE**
- **ANNUAL STATUS REPORT OF POSTMARKETING COMMITMENTS**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on August 10, 2009, amended on August 14, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of patients' understanding of the serious 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

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 022210 REMS ASSESSMENT**

- **NEW SUPPLEMENT FOR NDA 022210**
  - **PROPOSED REMS MODIFICATION**

  - **REMS ASSESSMENT**

- **NEW SUPPLEMENT FOR (NEW INDICATION FOR USE) FOR NDA 022210**
  - **REMS ASSESSMENT**
  - **PROPOSED REMS MODIFICATION (if included)**

- If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call 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: Package Insert, Medication Guide, REMS

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

/s/

JULIE G BEITZ
08/27/2009