# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-689**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-689

AstraZeneca LP
Attention: George Kummeth
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

Please refer to your new drug application (NDA) dated September 10, 2003, received September 10, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium® I.V. (esomeprazole sodium) for Injection, 20 and 40 mg.

We acknowledge receipt of your submissions dated December 18, 2003, January 8, February 10, March 29 and 30, April 1 and 9, May 6 and 26, and June 23 and 24, 2004.

We completed our review of this application, as submitted, and it is approvable. Before the application may be approved the following deficiencies need to be addressed:

1. Regarding your proposed drug product specifications:

   a- Your proposed acceptance criteria for total and individual impurities appear to be broad. Tighten the limits for total and individual impurities based on your real time stability test data (refer to your long term stability test data after — months which are submitted in amendment dated April 01, 2004).

   b- Your proposed acceptance criteria for residual solvents are broad. Tighten the limits based on your batch test data.

2. Provide information describing the structural elucidation of the impurities and degradants for your drug substance, drug product and reconstituted solutions. Of particular concern is the new impurity — which was discovered and reported in a recent amendment dated April 01, 2004. Reference standards are needed to support the proposed structures for the impurities and degradants.

3. Provide data documenting the level of degradants during reconstitution studies at different time points (please refer to the meeting minutes sent you by the Agency on May 26, 2004).

4. If the data (from question 1) confirms that Nexium IV is chemically unstable in Lactated Ringer's Injection and Dextrose Injection then further testing with these diluents is not required. The drug will need to be appropriately labeled in concordance with the data.

5. Additional compatibility studies using saline as your diluent and employing IV bags of all commercial compositions should be conducted and include the tubing, connectors, syringes, etc. supplied by these different manufacturers.

6. On-going compatibility studies for the drug product with various diluents, indicate that heavy metal specifications (test and limits of ———, need to be added to the drug substance and drug product specifications.

7. Three printed copies of methods validation should be provided. These copies should be prepared as per FDA guideline "GUIDELINE FOR SUBMITTING SAMPLES AND ANALYTICAL DATA FOR METHODS VALIDATION".

In addition, we have the following recommendations regarding expiry dating for the drug substance and drug product:

- We recommend an expiration date for the drug product of 24 months based on — months real time stability data pending acceptable responses to deficiencies 2 and 4.

- We recommend a retest period for the drug substance of ——— based on the ——— real time stability data pending acceptable responses to deficiencies 2 and 4.

Please note that we will be addressing your proposed label in a subsequent review cycle.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be 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.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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.

Under 21 CFR 314.102(d), you may request an informal 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, please call Melissa Hancock Furness, Regulatory Health Project Manager, at (301)-827-7450.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Joyce Korvick
7/9/04 01:43:19 PM
for Dr. Robert Justice

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: 03/23/05**

| **To: George Kummeth** | **From: Melissa Hancock Furness** |
|---|---|
| **Company:** Astra-Zeneca | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 302-886-2822 | **Fax number:** 301-443-9285 |
| **Phone number:** 302-885-8415 | **Phone number:** 301-827-7450 |

**Subject:** NDA 21-689 – Labeling Comments and Marked-up Package Insert

**Total no. of pages including cover**: 20

**Comments:**

# 18 Page(s) Withheld

_____ Trade Secret / Confidential

_X_ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Approvable Letter-1*

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

/s/

Melissa Furness
3/23/05 05:28:59 PM
CSO

Melissa Furness
3/23/05 05:32:08 PM
CSO