

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 21-153/ 21-154**

**APPROVAL LETTER**



NDA 21-153  
NDA 21-154

AstraZeneca LP  
Attention: Kathryn D. Kross  
725 Chesterbrook Blvd.  
Mailcode: E-2C  
Wayne, PA 19087-5677

Dear Ms. Kross:

Please refer to your new drug application (NDA 21-153) dated December 3, 1999, received December 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 13 and December 22, 1999; January 19, January 31, March 3, March 17, April 3, April 27, June 1, June 5, June 23, July 17, August 2, August 4, August 14, August 16, August 25, October 6, October 13, October 16, October 19, November 20, December 19, and December 20, 2000; and February 5, February 8, and February 15, 2001. Your submission of December 19, 2000 constituted a complete response to our December 15, 2000 action letter.

This new drug application provides for the use of Nexium (esomeprazole magnesium) Delayed-Release Capsules for the following: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; and 3) treatment of symptomatic gastroesophageal reflux disease.

Please also refer to your new drug application (NDA 21-154) dated February 28, 2000, received February 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated April 12, June 6, June 21, August 9, and November 17, 2000. Your submission of December 19, 2000 constituted a complete response to our December 15, 2000 action letter.

This application provides for the use of Nexium (esomeprazole magnesium) Delayed-Release Capsules in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the applications are approved

effective on the date of this letter. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton as submitted on October 6, 2000 and amended on November 20, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL to each NDA as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved NDA 21-153 and NDA 21-154." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We acknowledge your April 27, 2000 proposed pediatric drug development plan for symptomatic gastroesophageal reflux disease in patients 2 to 16 years of age (NDA 21-153). Your proposed plan includes a request for a waiver of the pediatric study requirement for this indication in patients less than 2 years of age. The Division is currently reviewing the appropriateness of pediatric studies for: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; and 3) treatment of symptomatic gastroesophageal reflux disease. We are deferring submission of the pediatric study reports until March 1, 2004.

We also acknowledge your May 8, 2000 request for a waiver from pediatric development of esomeprazole magnesium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease (NDA 21-154). For this indication, we are waiving the pediatric study requirement for pediatric patients less than 2 years of age as the necessary studies may be impossible or highly impractical to conduct because the number of patients is too small. We are deferring submission of your pediatric study reports in pediatric patients 2 years of age and older for this indication until March 1, 2004. Please submit your pediatric drug development plans within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. We acknowledge your April 27, 2000 "Proposed Pediatric Study Request" (PPSR) submitted under IND —. We are reviewing your submission and will respond to your proposal in a separate letter. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does

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not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to each 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, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to NDA 21-153 for this drug product, not to NDA 21-154. This includes the quarterly periodic adverse drug experience reports. In the future, no submissions should be made to NDA 21-154 except for the 20 copies of the final printed labeling, as requested above.

If you have any questions, call Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017 or Leo Chan R.Ph., Regulatory Project Manager at (301) 827-2127.

Sincerely,

*[See appended electronic signature page]*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

*[See appended electronic signature page]*

Mark J. Goldberger, M.D., M.P.H.  
Director  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

-----  
Lilia Talarico  
2/20/01 04:31:31 PM

Renata Albrecht  
2/20/01 05:28:07 PM  
for Mark Goldberger

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 21-153/ 21-154**

**APPROVABLE LETTER**



NDA 21-153  
NDA 21-154

DEC 15

AstraZeneca LP  
Attention: Gary P. Horowitz, Ph.D.  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Dr. Horowitz:

Please refer to your new drug application (NDA 21-153) dated December 3, 1999, received December 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 13 and December 22, 1999; and January 19, January 31, March 3, March 17, April 3, April 27, June 1, June 5, June 23, July 17, August 2, August 4, August 14, August 16, August 25, October 6, October 13, October 16, October 19, and November 20, 2000. Your submission of October 16, 2000 (together with your submission of October 6, 2000) constituted a complete response to our October 3, 2000 action letter.

This application provides for the following proposed indications: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; and 3) treatment of symptomatic gastroesophageal reflux disease.

Please also refer to your new drug application (NDA 21-154) dated February 28, 2000, received February 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated April 12, June 6, June 12, and November 17, 2000.

This application provides for the use of omeprazole magnesium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

We have completed the review of these applications as amended, and they are approvable. Before these NDAs may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

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We also have the following comments regarding the container labels and expiration date for the drug product:

1. All proposals regarding the package labels included in your November 20, 2000 amendment to NDA 21-153 are acceptable.
2. The stability data submitted support an expiration date of 24 months.

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

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 Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Mark J. Goldberger, M.D., M.P.H.  
Director  
Division of Special Pathogen  
and Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

-----  
Lilia Talarico  
12/15/00 04:05:16 PM

Renata Albrecht  
12/15/00 04:14:14 PM  
for Mark Goldberger, M.D., M.P.H.

**APPEARS THIS WAY  
ON ORIGINAL**

OCT 3 2000

AstraZeneca LP  
Attention: Gary P. Horowitz, Ph.D.  
725 Chesterbrook Blvd.  
Mailcode: E-3C  
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your new drug application (NDA) dated December 3, 1999, received December 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 13 and December 22, 1999; and January 19, January 31, March 3, March 17, April 3, April 27, June 1, June 5, June 23, July 17, August 2, August 4, August 14, August 16, and August 25, 2000.

This new drug application provides for the following proposed indications: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; and 3) treatment of symptomatic gastroesophageal reflux disease.

We note that NDA 21-154 for Nexium (esomeprazole magnesium) Delayed-Release Capsules was submitted to the Division of Special Pathogen and Immunologic Drug Products on February 28, 2000 for the following proposed indication: eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

We have completed the review of NDA 21-153, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Regarding the drug substance impurities:

Provide descriptions of the methods for determination of the following materials, including validation data (Page 004-002-056):

[ ]

Please be advised that the acceptability of not including tests for these possible impurities in the release specifications (e.g. not testing for \_\_\_\_\_ depends on complete information about the testing performed as part of the characterization of the drug

substance esomeprazole magnesium.

2. Provide data to demonstrate that the blister packaging used for the unit dose packages of 100 are child resistant.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed marked-up labeling (text for the package insert). Please note that the proposed indication for the eradication of *Helicobacter pylori* is not addressed in the enclosed labeling (affected text appears in gray). This indication and all sections of the labeling that pertain to this indication are currently under review by the Division of Special Pathogen and Immunologic Drug Products and will be addressed under NDA 21-154.

We also have the following recommendations regarding the container labels and the unit dose blister package:

1. The following statement should be placed on all container labels if space permits:

“Each delayed-release capsule, for oral administration, contains esomeprazole magnesium trihydrate equivalent to 20 mg or 40 mg esomeprazole. In addition, each capsule contains the following inactive ingredients...”

2. The “net quantity” on all container labels should be relocated and not appear in conjunction with the established name so it is not confused for the product strength.
3. The established name should be revised on the unit dose blister package to read “Delayed-Release Capsule” rather than “Delayed-Release Capsules.”

We note that you have not provided labels for the \_\_\_\_\_ count physician samples.

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

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit 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, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application. notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

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 Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

**APPEARS THIS WAY  
ON ORIGINAL**

Sincerely,

*TSI*

*10/3/00*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-153  
HFD-180/Div. Files  
HFD-180/M. Walsh  
HFD-180/H. Gallo-Torres  
    A. Shaw  
    L. Zhou  
    J. Choudary  
HFD-870/S. Al-Fayuomi  
    S. Doddapaneni  
HFD-715/Y. Tsong  
    T. Permutt  
HFD-002/ORM  
HFD-103/ADRA  
HFD-42/DDMAC (with labeling)  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

**APPEARS THIS WAY  
ON ORIGINAL**

Drafted by: M. Walsh 9/25/00  
Initialed by: A. Shaw 9/28/00, 10/3/00  
              L. Zhou 9/25/00, 9/28/00  
              J. Choudary 9/27/00  
              S. Aurecchia 10/2/00, 10/3/00  
Revised: M. Walsh 10/2/00, 10/3/00  
final: M. Walsh 10/3/00  
filename: \_\_\_\_\_

APPROVABLE (AE)

There are no phase 4 commitments.

**APPEARS THIS WAY  
ON ORIGINAL**