# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20988**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-988

MAR 22 2001

Wyeth-Ayerst Laboratories
Attention: Caroline Henesey, PhD
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Henesey:

Please refer to your new drug application (NDA) dated July 20, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix® I.V. (pantoprazole sodium) for Injection, equivalent to 40 mg.

We acknowledge receipt of your submissions dated November 3, December 14, 2000, and January 19, February 21, 22, and 26, March 6, 7, 15, and 16, 2001. Your submission of January 19, 2001 constituted a complete response to our November 2, 2000 action letter.

This new drug application provides for the use of Protonix® I.V. (pantoprazole sodium) for Injection for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), **as an alternative to oral therapy in patients who are unable to take Protonix® (pantoprazole sodium) Delayed-Release Tablets**. Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

We have completed the review of this application, 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 application is 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 draft labeling (immediate container and carton labels submitted March 15, 2001). 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 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, this submission should be designated "FPL for approved NDA 20-988." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated February 26, 2001 and your facsimile dated March 21, 2001. These commitments are listed below.

1. To provide assurance that an in-line filter is being used during the administration of this product (letter dated February 26, 2001). The time frame for this commitment is 1 year after NDA approval date.

2. To provide a complete physical and chemical characterization of the [redacted] identify the conditions that promote precipitation and identify what other types of substances or combinations of substances in the diluent solutions (other ions, other drugs, etc) can cause precipitation. The time frame for this commitment is 1 year after NDA approval date (facsimile dated March 21, 2001).

3. To conduct studies comparing commonly used diluents (saline, lactated ringers, D5W) on precipitate formation. The time frame for this commitment is 1 year after NDA approval date (facsimile dated March 21, 2001).

4. To provide a proposal to eliminate the filtration requirement for the product, i.e. reformulation. The time frame for this commitment is 2 years after NDA approval date (facsimile dated March 21, 2001).

5. To revise the packaging, i.e. to co-package one vial and one filter per box. We note that the investigations of filter stability at 2°C-8°C have been initiated. The time frame for this commitment is 2 years after NDA approval date (facsimile dated March 21, 2001).

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. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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 January 19, 2001 proposed pediatric plan for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative to oral therapy in patients who are unable to take Protonix® (pantoprazole sodium) Delayed-Release Tablets in patients 2 to 16 years of age. We are deferring submission of the pediatric study reports until April 1, 2004.

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) for details. We acknowledge your January 19, 2001 "Proposed Pediatric Study Request" (PPSR). 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 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 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

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7475.

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

Enclosure: Package Insert Labeling Text

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20988**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-988

Wyeth-Ayerst Laboratories
Attention: Caroline Henessey
P.O. Box 8299
Philadelphia, PA 19101-8299

NOV - 2 2000

Dear Ms. Henessey:

Please refer to your new drug application (NDA) dated July 20, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix® I.V. (pantoprazole sodium) for Injection.

We acknowledge receipt of your submissions dated February 22, May 2 and 3, June 23, August 30, September 8, and October 6, 2000. Your submission of May 2, 2000 constituted a complete response to our February 24, 2000 action letter.

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

1. Revise the specification to a level that does not exceed the content in actual production or pilot batches which conform to the visual "Clarity of Reconstituted Solution" test, the USP particulates test, and the assay requirement.

2. Modify the container such that a vial of PROTONIX I.V. and a filter are contained in the same package.

In addition, it will be necessary for you to submit draft labeling for the package insert (PI) identical in content to that submitted on June 23, 2000, revised as follows:

Additional revisions to the labeling regarding the **DOSAGE AND ADMINISTRATION** section will be conveyed to you following our review of the modified packaging being requested.

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

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-40
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 Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7475.

Sincerely,

CT 11-2-00

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-988

Food and Drug Administration
Rockville MD 20857

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

FEB 24 2000

Dear Dr. DeLorme Sullivan:

Please refer to your new drug application (NDA) dated July 20, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix I.V. (pantoprazole sodium) for Injection.

We acknowledge receipt of your submissions dated October 21, 1998; March 8, May 11, May 13, June 9, and August 31, 1999; and January 19, 2000. Your submission of August 31, 1999 constituted a complete response to our July 20, 1999 action letter.

We also refer to your submission dated February 16, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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

1. Conduct studies and provide the results to identify the cause of the instability of the drug product in [ ] containers as well as the nature of the particulates.

2. Provide data demonstrating the compatibility of the admixtures in PVC containers from a number of manufacturers.

3. Provide data demonstrating the compatibility (or incompatibility) of the admixtures in commercially available containers which are composed of materials other than PVC or [ ]

4. Provide data demonstrating the compatibility of the reconstituted product and its admixtures for all materials with which the solutions could come into contact during use (i.e. tubing, connectors, syringes, etc.).

5. Photostability studies to justify the labeling statement that neither the reconstituted nor the admixed solutions need to be protected from light were conducted only in Dextrose solution. Conduct studies in Sodium Chloride and Lactated Ringer's solutions and provide the results.

In addition, it will be necessary for you to submit draft labeling identical in content to the enclosed marked-up text. Additional revisions to the labeling regarding the incompatibility of the drug product in certain containers will be addressed in the next review cycle.

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-40
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.

Sincerely,

/S/

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

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-988

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O: Box 8299
Philadelphia, PA 19101-8299

JUL 20 1999

Dear Dr. DeLorme Sullivan:

Please refer to your new drug application (NDA) dated July 20, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium sesquihydrate) for Injection.

We acknowledge receipt of your submissions dated October 21, 1998; March 8, May 11, May 13, and June 9, 1999.

We have completed the review of this application, as amended, and it is approvable for the short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative in patients who are unable to continue taking Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets. Safety and efficacy of Protonix for Injection as an initial treatment for GERD have not been established. Therefore, before this application may be approved it will be necessary to obtain approval for NDA 20-987, Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets. In addition, it will be necessary for you to address the following:

Labeling

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

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

Chemistry, Manufacturing, and Controls

3. Testing:

   Please provide a brief product-specific sampling plan for in-process testing of samples and finished product; this information could not be located in the submission.

4. Stability:

   The proposed stability testing schedule for batches manufactured in the second and subsequent years of production is not acceptable. Use a full testing schedule (same as proposed for first year) until an adequate manufacturing history is established. Submit a revised protocol.

Based on the 12-month stability data that have been provided, only an 18-month expiration date is appropriate at this time. If you wish to extend expiry, please provide a stability protocol in a prior approval supplement.

Please provide three separate methods validation packages including a list of samples that will be submitted.

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 send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Although not required for approval of this indication, in order to bridge Protonix for Injection to other antisecretory drug products, you should consider conducting the appropriate clinical trials to assess the efficacy of intravenous pantoprazole for *de novo* treatment of erosive esophagitis and GERD, and/or to show pharmacodynamic equivalence of intravenous pantoprazole and other antisecretory drug products on inhibition of gastric acid secretion.

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

Sincerely,

/S/

Victor Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research