CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: September 21, 2000
DUE DATE: September 29, 2000
OPDRA CONSULT #: 00-0253

TO: Lilia Talarico, M.D.
    Director, Division of Gastro-Intestinal and Coagulation Drug Products
    HFD-180

THROUGH: Maria Walsh, Project Manager
          HFD-180

PRODUCT NAME: Nexium (Esomeprazole Magnesium Delayed-Release Tablets)
                20 mg and 40 mg

NDA #: 21-153

MANUFACTURER:
Manufactured by:
    AstraZeneca AB
Distributed by:
    Astra Pharmaceuticals, L.P.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Gastro-Intestinal Drug Products (HFD-180), OPDRA reevaluated the acceptability of the proposed trade name Nexium and reviewed the proposed container labels, carton and insert labeling, for possible interventions that may help minimize medication errors.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the name, “Nexium”. We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

☑ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

/S/ Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

10/2/00
REQUEST FOR CONSULTATION

TO (Division/Office): HFD-400 (OPDRA), Attention: Jerry Phillips; Franklawn Bldg. Rm. 15B03
FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products)
DATE OF DOCUMENT: 4/3/00 and 12/3/99

DATE: July 11, 2000
IND NO.: NDA NO.: 21-153

NAME OF DRUG: Nexium (esomeprazole magnesium) Delayed-Release Capsules
PRIORITY CONSIDERATION: CLASSIFICATION OF DRUG: 2S

NAME OF FIRM: AstraZeneca LP
DESIRED COMPLETION DATE: 9/4/00

REASON FOR REQUEST

I. GENERAL
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ RESPONSE TO DEFICIENCY LETTER
☐ PROTOCOL REVIEW ☐ END OF PHASE II MEETING ☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE ☐ RESUBMISSION ☐ LABELING REVISION
☐ DRUG ADVERTISING ☐ SAFETY/EFFICACY ☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT ☐ PAPER NDA ☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION ☐ CONTROL SUPPLEMENT ☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY

II. BIOMETRICS

<table>
<thead>
<tr>
<th>STATISTICAL EVALUATION BRANCH</th>
<th>STATISTICAL APPLICATION BRANCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ TYPE A OR B NDA REVIEW</td>
<td>☐ CHEMISTRY REVIEW</td>
</tr>
<tr>
<td>☐ END OF PHASE II MEETING</td>
<td>☐ PHARMACOLOGY</td>
</tr>
<tr>
<td>☐ CONTROLLED STUDIES</td>
<td>☐ BIOPHARMACEUTICS</td>
</tr>
<tr>
<td>☐ PROTOCOL REVIEW</td>
<td>☐ OTHER</td>
</tr>
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</table>

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES ☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a follow-up consult request for evaluation of the proprietary tradename: Nexium (esomeprazole magnesium) Delayed-Release Capsules. The original review of this proprietary name (dated 11/29/99) was conducted under IND —— attached. The sponsor has since submitted the NDA for this proposed drug product and the 10-month goal date is 10/3/00. Please re-evaluate the proposed proprietary name to determine if there are other names that would render Nexium objectionable. Attached is the current draft labeling (submitted 4/3/00) and the container labeling (submitted 12/3/99).

:: Original NDA 21-153
HFD-180/Div. Files
HFD-180/M.Walsh

SIGNATURE OF REQUESTER: METHOD OF DELIVERY (Check one):
☐ MAIL ☐ HAND
APPEARS THIS WAY ON ORIGINAL
CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: November 17, 1999  DUE DATE: N/A  OPDRA CONSULT #: 99-073

TO (Division):
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

PRODUCT NAMES: Nexium™
(Esomeprazole Magnesium)

MANUFACTURER: AstraZeneca LP

IND#: —

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Gastro-Intestinal and Coagulation Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, Nexium™, with other approved proprietary/generic names. This review includes studies conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA does not object to the use of the proposed proprietary name, Nexium™. See review.

/S/    11/25/99
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-5189

/S/    11/30/99
Fred Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 15, 2001

TO: NDA 21-153

FROM: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

SUBJECT: Revised Draft Labeling
NDA 21-153, Nexium (esomeprazole magnesium) Delayed-Release Capsules

NDA 21-153 was submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) on December 3, 1999 and 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 (GERD).

The sponsor submitted revised draft labeling immediately following the February 12, 2001 meeting between FDA and the sponsor. The Agency reviewed and revised the draft labeling. The revised version was faxed to the sponsor on February 13, 2001.

NEXIUM™
(esomeprazole magnesium)
DELAYED-RELEASE CAPSULES

Rx only

DESCRIPTION
WITHHOLD 23

Draft

Labeling
/s/

Maria Wal
2/15/Cl
CSO

APPEARS THIS WAY
ON ORIGINAL
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 1, 2001

TO: NDA 21-153

FROM: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

SUBJECT: Final Revised Draft Labeling
NDA 21-153, Nexium (esomeprazole magnesium) Delayed-Release Capsules

NDA 21-153 was submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) on December 3, 1999 and 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 (GERD).

The sponsor submitted revised draft labeling dated December 19, 2000 in response to the approvable letter dated December 15, 2000. The Agency reviewed and revised the draft labeling. The revised version below was faxed to the sponsor on February 1, 2001.
WITHHOLD 28

Draft

Labeling
DATE: January 31, 2001

TO: NDA 21-153 and NDA 21-154

FROM: Maria R. Walsh, M.S., Regulatory Project Manager. HFD-180

SUBJECT: Revised Draft Labeling
Nexium (esomeprazole magnesium)
Delayed-Release Capsules

NDA 21-153 was submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) on December 3, 1999 and 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.

NDA 21-154 was submitted to the Division of Special Pathogen and Immunologic Drug Products (HFD-590) on February 28, 2000 and provides for the following proposed indication: use of 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.

The sponsor submitted revised draft labeling dated December 19, 2000 in response to the approvable letter dated December 15, 2000 for NDA 21-153 and NDA 21-154. The submitted draft labeling was reviewed and revised by the biopharmaceutics teams of both Divisions (see revisions to the CLINICAL PHARMACOLOGY, PRECAUTIONS, Information for Patients/Drug Interactions, and DOSAGE AND ADMINISTRATION sections of the labeling below).
WITHHOLD

Draft

Labeling
NDA 21-153

DISCIPLINE REVIEW LETTER

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We also refer to your submission dated December 20, 2000 which contained your response to our November 29, 2000 chemistry discipline review letter.

Our review of your submission is complete, and we have identified the following deficiencies:

[Signature]
We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
/s/                      
---------------------
Liang Zhou
1/12/01 07:03:44 PM

APPEARS THIS WAY
ON ORIGINAL
NDA 21-153

AstraZeneca LP
Attention: Kathryn D. Kross
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Horowitz:

We acknowledge receipt on December 20, 2000 of your December 19, 2000 resubmission to your new drug application (NDA) for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

This resubmission contains revised draft labeling submitted in response to our December 15, 2000 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is February 20, 2001.

If you have any questions, call me at (301) 443-8017.

Sincerely,

Maria R. Walsh, M.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
/s/

---------------------
Maria Walsh
1/4/01 10:35:05 AM

APPEARS THIS WAY
ON ORIGINAL
Dear Dr. Horowitz:

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

We also refer to your submissions dated October 6, October 13, October 16, and October 19, 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

[signature]
We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
/s/

-------------------------------
Liang Zhou
11/29/00 11:23:19 AM

APPEARS THIS WAY
ON ORIGINAL
NDA 21-153

AstraZeneca LP
Attention: Kathym D. Kross
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Kross:

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

We also refer to your submissions dated October 6 and October 16, 2000 which contained your response to our October 3, 2000 action letter.

We are reviewing the labeling contained in your submissions and have the following comments. We need your prompt written response to continue our evaluation of your NDA.

1. LABELS
2. PACKAGE INSERT

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

/S/
Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
AstraZeneca LP
Attention: Kathyrn D. Kross
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Kross:

We acknowledge receipt on October 17, 2000 of your October 16, 2000 resubmission to your new drug application (NDA) for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

This submission, along with your amendment dated October 6, 2000, contains additional chemistry and labeling information submitted in response to our October 3, 2000 action letter.

We consider the October 17, 2000 submission a complete class 1 response to our action letter. Therefore, the primary user fee goal date is December 15, 2000.

If you have any questions, call me at (301) 443-8017.

Sincerely,

/S/

10/25/00

Maria R. Walsh, M.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We also refer to your submissions dated April 3, June 1, June 23, July 17, August 2, and August 25, 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies (all page numbers cited refer to your April 3, 2000 amendment, except as noted):

I. Regarding the drug substance:
WITHHOLD 5
III. Regarding the labeling:

Change the text of the "Description" as follows:

A. Change the text from

______ is the S-isomer of omeprazole."

to

"Esomeprazole is the S-isomer of omeprazole."
B. Change the molecular formula from:

"C_{14}H_{36}N_{8}O_{6}S_{2}Mg \times 3H_{2}O"

to

"(C_{11}H_{18} N_{3}O_{3}S)_{2}Mg \times 3H_{2}O"

IV. Regarding the methods validation:

Provide reference standards and samples that will be valid at the time samples are submitted for methods validation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

/\S/  9/27/05
Liang Zhou, Ph.D.
Chemistry Team Leader for the
    Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
DNDC II. Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
Dear Ms. Kross

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

We are reviewing the Chemistry section of your submission and have identified deficiencies in a Drug Master File (DMF) for the drug product. We are hereby notifying you that a deficiency letter, dated July 25, 2000, has been issued to ___________ for DMF ___________.

Per the user fee authorization agreements, the comments issued to the DMF holder do not reflect a final decision on the information reviewed in your application and should not be construed to do so. We may identify other information that must be provided prior to approval of this application. If the DMF holder chooses to respond to the issues raised in the deficiency letter during this review cycle, depending on the timing of their response, as per the user fee reauthorization agreements, we may or may not be able to consider their response prior to taking an action on your application during this review cycle.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

/S/

Liang Zhu, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
INFORMATION REQUEST LETTER

JUL 19 2000

AstraZeneca LP
Attention: Kathryn D. Kross
Mailcode: E-3C
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Ms. Kross:

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

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

The analytical methods validation report is incomplete. Please submit a complete assay methods validation report that includes the following:

1. A table listing all the Clinical Pharmacology and Biopharmaceutics-related studies and the analytical method(s) used in each study.

2. A complete assay validation for each analytical method (i.e. specificity, linearity, sensitivity, stability of the samples, accuracy, and precision for the drug and metabolites).

If you have any questions, call Maria R. Walsh, M.S., Project Manager at (301) 443-8017.

Sincerely,

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL
MEMORANDUM OF TELECON

DATE: July 17, 2000

APPLICATION NUMBER: NDA 21-153; Nexium (esomeprazole magnesium) Delayed-Release Capsules

BETWEEN:
Name: Ms. Kathy Kross, Regulatory Affairs
Phone: (610) 695-1873
Representing: AstraZeneca LP

AND
Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products. HFD-180

SUBJECT: Clarification re: Clinical Pharmacology Studies

BACKGROUND: I called Ms. Kross on July 12, 2000 per the biopharmaceutics reviewer. Dr. Suliman Al-Fayoumi, and asked her whether the ___ formulation used in Study DC-QBE-002 is the same as that used in Study SH-QBE-0035. We note that the batch numbers used in the two studies are different, i.e. batch # H1365 vs batch #H1356, respectively. Ms. Kross said she would check into this and get back to me.

TODAY'S CALL: Ms. Kross called and confirmed that the same ___ formulations were used in both studies. The batch number for both studies is H1365. The batch number recorded for Study SH-QBE-0035 (i.e. H1356) contains a typographical error. The call was then concluded.

/S/ 1/31/00
Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 21-153
HFD-180/Div. File
HFD-180/PM/M.Walsh
HFD-870/A.Al-Fayoumi
S.Dodapaneni

filename: ___________________

TELECON
INFORMATION REQUEST LETTER

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

Dear Dr. Horowitz:

Please refer to your December 3, 1999 new drug application for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We are reviewing the chemistry section of your submission and have the following information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide a Letter of Authorization (LOA) for the resins used to manufacture the bottles.

2. For the following Drug Master Files (DMFs), please provide a LOA referencing the specific products used:
   A. DMF —— amendment dated November 18, 1998).
   C. DMF —— amendment dated October 9, 1998).

3. For the following DMFs, please provide a LOA referencing the specific date of the amendment containing the information for the specific product used:
   A. DMF ——
   B. DMF ——

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

/S/
Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your December 3, 1999 new drug application for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We also refer to our acknowledgement letter dated December 8, 1999. We wish to correct several errors in that letter regarding the date of receipt and the user fee goal dates. The date of receipt of your NDA is December 3, 1999. The primary user fee goal date is October 3, 2000 and the secondary user fee goal date is December 3, 2000.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

/S/ 1/5/00

Maria R. Walsh, MS
Regulatory Project Manager
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/PM/M.Walsh

final: M.Walsh 1/5/00
filename: ————

ADVICE (AD)
AstraZeneca LP  
Attention: Gary P. Horowitz, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Horowitz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nexium (esomeprazole magnesium) Delayed-Release Capsules

Therapeutic Classification: Standard (S)

Date of Application: December 3, 1999

Date of Receipt: December 6, 1999

Our Reference Number: NDA 21-153

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 4, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 6, 2000 and the secondary user fee goal date will be December 6, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

**U.S. Postal/Courier/Overnight Mail:**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857
If you have any questions, contact me at (301) 443-8017.

Sincerely,

/ S / 12/8/99

Maria R. Walsh, M.S.
Regulatory Project Manager
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/PM/M.Walsh
DISTRICT OFFICE

final: M.Walsh 12/8/99
filename: ____________

ACKNOWLEDGEMENT (AC)
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 2, 2000

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Correction to Review Dated September 21, 2000

TO: NDA 21-153

In the Executive Summary on Page 3 of the above review under II. A. 1. it should read as follows:

172 [H40 mg (n=654) vs H20 mg (n=656) vs O20 mg (n=650)] instead of 172 [H40 mg (n=—) vs H20 mg (n=656) vs O20 mg (n=650)]

cc: HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-705/TPermutt
HFD-705/YTSong
HFD-40/PStaub
HFD-180/JChoudary
HFD_180/LZhou
f/t 10/2/00 jgw

Appears this way on original

October 3, 2000

Hugo E. Gallo-Torres, M.D., Ph.D.
Dear Dr. Riff:

Between May 10 and May 15, 2000, Ms. Diane C. Van Leeuwen, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #222) of the investigational drug, Nexium (esomeprazole magnesium) Delayed-Release capsules performed for AstraZeneca LP. This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. In particular, we note instances of inaccurate and inadequate record keeping. For example, subject #05 had a history of skin cancer and herpes zoster that was not reported on the CRFs.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Van Leeuwen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855
David Chua, M.D.
1 South 280 Summit Avenue
Court A-1
Oakbrook Terrace, Illinois 60181

Dear Dr. Chua:

Between May 17 and May 23, 2000, Ms. Lisa A. Hornback and Ms. Lisa Hayka representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 173) of the investigational drug, Nexium™ (esomeprazole magnesium) Delayed-Release, performed for AstraZeneca. This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hornback and Investigator Hayka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY ON ORIGINAL
Howard Schwartz, M.D.
Miami Research Associates
7500 SW 87th Avenue, Suite #200
Miami, Florida 33176

*Dear Dr. Schwartz:

Between May 23 and May 30, 2000, Mr. Bill Tackett, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 222) of the investigational drug Nexium (esomeprazole magnesium) Delayed-Release performed for AstraZeneca. This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Tackett presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following: subject #006 was administered the study drug two days after the use of diazepam instead of waiting the 7 day washout period required by the protocol.

Please make appropriate corrections/changes in your procedures to assure that the finding noted above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Tackett during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/
John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY ON ORIGINAL
Dear Dr Breiter:

Between May 15 and 17, 2000, Mr. Anthony Warchut, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #173) of the investigational drug, Nexium (esomeprazole magnesium), performed for Astra-Zeneca LP. This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

At the close of the inspection, Investigator Warchut presented his inspectional observations listed on Form FDA-483 and discussed these observations with you and your staff. From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. In particular, we note that you failed to report in the CRF of subject #20 the adverse reactions of upper abdominal pain, nausea, diarrhea, and low chest pain which caused the subject to visit the emergency room on 12/16/97. These ADRs were not reported to the sponsor.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Warchut during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855
DATE: November 24, 2000

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21,153 (NEXIUM) – Amendment Dated October 16, 2000-
Sponsor’s Revised Draft Labeling.

TO: NDA 21,153

In amendment dated October 16, 2000, the sponsor submitted a revised draft labeling as part of response to the Division’s approvable letter dated October 3, 2000. In the present memorandum, portions of the labeling which relate to preclinical data are reproduced below as FDA version and Sponsor’s version. Our evaluations of the Sponsor’s revisions and the recommended final FDA versions follow. The following are the specific portions of the labeling.


2. “PRECAUTIONS”
   a. “Carcinogenesis, Mutagenesis, Impairment of Fertility” – on sponsor’s pages 33 and 34.
   b. “Pregnancy, Teratogenic Effects, Pregnancy category B.” – on sponsor’s page 34 and 35.
   c. “Nursing Mothers” - on sponsor’s page 37.

3. “OVERDOSAGE” – on sponsor’s page 42.

APPEARS THIS WAY
ON ORIGINAL
WITHHOLD 9 PAGES

Draft

Labeling
cc:
NDA
HFD-180
HFD-181/CSO/Ms. Walsh
HFD-180/Dr. Choudary
R/D typed by deg: 11/28/00
F/T deg: 11/30/00

APPEARS THIS WAY
ON ORIGINAL
/s/

Jasti Choudary
12/1/00 10:45:21 AM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL
DATE: September 15, 2000

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180


To: NDA 21,153

In amendment dated August 2, 2000, the sponsor submitted a revised draft labeling. In the present memorandum, portions of the labeling which relate to preclinical data are reproduced below (designated as sponsor’s version). Our evaluations of the sponsor’s versions and the recommended revisions follow. The following are the specific portions of the labeling:

1. “CLINICAL PHARMACOLOGY”
   “Enterochromaffin-like (ECL) cell Effects”- on Sponsor’s page 6.

2. “PRECAUTIONS”
   c. “Nursing Mothers” on sponsor’s page 23.
WITHHOLD 5 pages

Draft Labeling
cc:
NDA
HFD-180
HFD-181/CSO/Ms. Walsh
HFD-180/Dr. Choudary
F/t by deg: 9/18/00

APPEARS THIS WAY
ON ORIGINAL
PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

<table>
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<th>021153</th>
<th>Trade Name:</th>
<th>NEXIUM 20/40MG DELAYED RELEASE CAPSULES</th>
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</thead>
<tbody>
<tr>
<td>Supplement</td>
<td>000</td>
<td>Generic Name:</td>
<td>NEXIUM 20/40MG DELAYED RELEASE CAPSULES</td>
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<tr>
<td>Type:</td>
<td>N</td>
<td>Dosage Form:</td>
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<tr>
<td>Regulatory</td>
<td>AE</td>
<td>COMIS Indication:</td>
<td>TREATMENT OF EROSI VE ESOPHAGITIS/HEALING/MAINTENANCE/SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE</td>
</tr>
<tr>
<td>Action Date:</td>
<td>10/3/00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication # 1:</td>
<td>Healing of erosive esophagitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Label Adequacy:</td>
<td>Inadequate for ALL pediatric age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation Needed:</td>
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**Comments (if any):**

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<th>Date</th>
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<td>Deferred</td>
<td>2/20/01</td>
</tr>
<tr>
<td>2 years</td>
<td>16 years</td>
<td>Deferred</td>
<td></td>
</tr>
</tbody>
</table>

| Indication # 2: | Maintenance of healing of erosive esophagitis |
| Label Adequacy: | Inadequate for ALL pediatric age groups |
| Formulation Needed: |                                    |

**Comments (if any):**

<table>
<thead>
<tr>
<th>Lower Range</th>
<th>Upper Range</th>
<th>Status</th>
<th>Date</th>
</tr>
</thead>
</table>

| Indication # 3: | Treatment of symptomatic gastroesophageal reflux disease |
| Label Adequacy: | Inadequate for ALL pediatric age groups |
| Formulation Needed: | NEW FORMULATION needed. Applicant NOT WILLING to provide it. |

**Comments (if any):**

<table>
<thead>
<tr>
<th>Lower Range</th>
<th>Upper Range</th>
<th>Status</th>
<th>Date</th>
</tr>
</thead>
</table>

This page was last edited on 2/15/01

Maria Walsh

Signature

2/15/01
Other Labeling In Class:

Prilosec (omeprazole)

Prevacid (lansoprazole)
Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol and slightly soluble in aqueous and propylene glycol very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid and media but has acceptable stability under alkaline conditions. PRILoseC® Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that desorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 1 to 3 hours. Peak plasma concentrations of omeprazole are about 8 to 9 times the plasma level of acid produced by the 15-day basal acid output in healthy subjects (24 hr); peak plasma levels of 5-methyl-5H-Imidazole-4-carboxylic acid occur 1 to 2 hours after the peak plasma levels of omeprazole. The plasma level of omeprazole is rapidly reduced by metabolic and excretory pathways in the liver and kidneys, and approximately 80% of an oral dose is excreted in the urine. The plasma half-life of omeprazole is about 0.5 hours.

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism: Omeprazole
PRILoseC® Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that desorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 1 to 3 hours. Peak plasma concentrations of omeprazole are about 8 to 9 times the plasma level of acid produced by the 15-day basal acid output in healthy subjects (24 hr); peak plasma levels of 5-methyl-5H-Imidazole-4-carboxylic acid occur 1 to 2 hours after the peak plasma levels of omeprazole. The plasma level of omeprazole is rapidly reduced by metabolic and excretory pathways in the liver and kidneys, and approximately 80% of an oral dose is excreted in the urine. The plasma half-life of omeprazole is about 0.5 hours.

Clinical Studies
DuoDental Ulcer Disease
Active DuoDental Ulcer—In a multicenter double-blind placebo-controlled study of 147 patients with endoscopically documented duo-dental ulcer, the percentage of patients treated (per protocol) at 2 and 4 weeks with PRILoseC® 20 mg once a day had a mean difference of 71.7% compared to placebo (p < 0.01).

Treatment of Active DuoDental Ulcer

<table>
<thead>
<tr>
<th>Week</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Placebo</td>
</tr>
<tr>
<td>4</td>
<td>PRILoseC® 20 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Complete daytime and nighttime pain relief occurred significantly faster (p < 0.01) in patients treated with PRILoseC® 20 mg than in patients treated with placebo at the end of the study, significantly more patients who had received PRILoseC® had complete relief of daytime pain at 4 weeks after treatment (p < 0.01). In a multicenter double-blind study of 293 patients with endoscopically documented duo-ulcer disease, the percentage of patients treated (per protocol) at 4 weeks with PRILoseC® 20 mg once a day had a mean difference of 71.7% compared to placebo (p < 0.01).

Treatment of Active DuoDental Ulcer

<table>
<thead>
<tr>
<th>% of Patients Healed</th>
<th>Placebo</th>
<th>PRILoseC® 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>Week 4</td>
<td>42</td>
<td>83</td>
</tr>
</tbody>
</table>

Healing occurred significantly faster in patients treated with PRILoseC® than in those treated with simbline 30 mg (p < 0.01) in a prospective randomized double-blind study of 105 patients with endoscopically documented duo-ulcer disease. 20 mg and 40 mg of PRILoseC® were compared to 150 mg and 30 mg of simbline at 2, 4, and 8 weeks. After 4 weeks both doses of PRILoseC® were statistically superior (p < 0.01) to simbline, and 40 mg was not superior to 20 mg of PRILoseC®.

Prolonged Treatment: 48 and 56 weeks

| Weeks 48 | 80.0% | 92.0% |
| Weeks 56 | 87.5% | 94.0% |

<table>
<thead>
<tr>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Healing occurred significantly faster in patients treated with PRILoseC® than those treated with simbline 30 mg (p < 0.01) in a prospective randomized double-blind study of 105 patients with endoscopically documented duo-ulcer disease. The percentage of patients treated (per protocol) at 4 weeks with PRILoseC® was significantly higher (p < 0.01) than the percentage of patients treated with simbline.

Quantitative assessment of interindividual variability in the pharmacokinetics of omeprazole was performed using microdialysis and chronic indwelling catheters. In 10 subjects, plasma and duodenal fluid samples were collected and analyzed (per protocol) for omeprazole, 5-methyl-5H-Imidazole-4-carboxylic acid, and 5-methyl-5H-Imidazole-4-carboxylic acid N-acetyl conjugate in plasma and duodenal fluid. The interindividual variability of omeprazole plasma concentrations was found to be approximately 30% for each of the three time points. The interindividual variability of the 5-methyl-5H-Imidazole-4-carboxylic acid plasma concentrations was found to be approximately 25% for each of the three time points. The interindividual variability of the 5-methyl-5H-Imidazole-4-carboxylic acid N-acetyl conjugate plasma concentrations was found to be approximately 30% for each of the three time points.
In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD in comparison with histamine 
H₂-receptor antagonists in patients with erosive esophagitis, grade 2 or above. PRILOSEC in a dose of 20 mg was significantly more effective than the active control, Complete Symptom and nighttime heartburn relief occurred significantly faster (p < 0.01) in patients treated with PRILOSEC than in those taking placebo or histamine H₂-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg esomeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

**Long-term Maintenance Treatment of Esophageal Erosions**

In a U.S. double-blind, randomized multicenter controlled study, two dose regimens of PRILOSEC were studied in patients with endoscopically confirmed healed erosions. Results to determine maintenance of healing of erosive esophagitis are shown below.

**Life Table Analyses**  

<table>
<thead>
<tr>
<th>Dose</th>
<th>PRILOSEC 20 mg q.d.</th>
<th>Placebo 20 mg q.d.</th>
<th>Number of Patients</th>
<th>Number of Erosions</th>
<th>Number of Erosions</th>
<th>Number of Patients</th>
<th>Number of Erosions</th>
<th>Number of Erosions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRILOSEC 20 mg q.d.</td>
<td>344</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
</tr>
<tr>
<td>Placebo 20 mg q.d.</td>
<td>191</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
</tr>
</tbody>
</table>

*Percent in erosive remission at 12 months:*

- **PRILOSEC 20 mg q.d.**: 77% (n = 331)
- **PRILOSEC 10 mg q.d.**: 58% (n = 331)
- **Ranitidine 150 mg b.i.d.**: 46% (n = 331)

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of PRILoseC was effective, while 10 mg did not demonstrate efficacy.

**Pathological Hypersecretory Conditions**

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine neoplasia, PRILoseC Delayed-Release Capsules significantly inhibited gastric acid and secretion in controlled associations of diarrhea, anemia, and pain. Doses ranging from 20 mg every other day to 10 mg every day maintained basal and daytime acid below 10 mmol/h in patients without prior gastric surgery, and below 5 mmol/h in patients with prior gastric surgery.

Tests doses are used for the individual patient need, and adjustments were necessary with time in some patients (see Doseage and ADMINISTRATION). PRILoseC was well tolerated at these high doses for prolonged periods (> 5 years). In 1977 most 267 patients, serum gastrin levels were not modified by PRILoseC. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with PRILoseC developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such lesions, rather than the result of the administration of PRILoseC. (See ADVERSE REACTIONS.)

**Microbiology**

Omeprazole and clarithromycin dual therapy and omeprazole clarithromycin and amoxicillin triple therapy have been shown to be active against most strains of Helicobacter pylori in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

**Helicobacter pylori**

**Treatment Resistance**

Clarithromycin pretreatment resistance rates were 3% (4/132) in the omeprazole clarithromycin dual therapy studies (M93-067, M93-103) and 9.3% (4/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (128, 127, M93-448). Amoxicillin pretreatment susceptible isolates (0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (128, 127, M93-448). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an uncontrolled pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by test.

**References**

1. Patients were included in the analysis if they had confirmed duodenal ulcer disease (lesions 139 and 127) and history of ulcer at 4 years. In 127 and 128 studies, patients were included if they completed the study. Additionally, if patients were not included in the analysis due to an adverse event related to the study, they were included in the analysis as failures of therapy. The impact of withdrawal on ulcer recurrence was not assessed in patients with a history of peptic ulcer.

2. Patients were included in the analysis if they had documented H. pylori infection at baseline and confirmed duodenal ulcer disease. All biopsies included were included as failures of therapy.

3. *p < 0.05* versus clarithromycin plus amoxicillin.

**Double Therapy (PRILoseC/Clostridium)**

- For randomized, double-blind, multicenter studies (M93-067, M93-103, M93-058) evaluated PRILoseC 40 mg q.d. plus clarithromycin 500 mg bid for 14 days.
- In 139 studies, patients were included in the U.S. and Canada and enrolled 242 and 258 patients, respectively. H. pylori infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 278 patients in Study M93-103. These studies compared the combination regimens to PRILoseC and clarithromycin monotherapies. Studies M93-111 and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. From placebo and clarithromycin on 14 days in patients M93-111 and 208 patients in Study M93-058. These studies compared the combination regimens to placebo and for efficacy analyses for patients with gastric or duodenal ulcers are described below. H. pylori eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment and two negative tests were required to be considered eradicated. In the per-protocol analysis, the following patients were excluded: patients with missing H. pylori test results, and patients who were not assessed for H. pylori eradication because they were found to have an ulcer at the end of treatment.

The combination of omeprazole and clarithromycin was effective in eradicating H. pylori.
**Prozac** (omeprazole) Delayed-Release Capsules

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

**Clarithromycin Susceptibility Results**

- Post-therapy susceptibility results: 1 μg/mL
- Post-therapy susceptibility results: 0 μg/mL

**Clarithromycin Post-therapy Results**

- Post-therapy susceptible: 8 μg/mL
- Post-therapy resistant: 0 μg/mL

**Dual Therapy (omeprazole 40 mg q.d. clarithromycin 500 mg q.d. for 14 days followed by omeprazole 20 mg q.d. for another 12 weeks):**

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 μg/mL</td>
<td>72%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>8 μg/mL</td>
<td>42%</td>
<td>15%</td>
<td>43%</td>
</tr>
<tr>
<td>6 μg/mL</td>
<td>96%</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Susceptible:** 10 μg/mL

**Intermediate:** 8 μg/mL

**Resistant:** 6 μg/mL

**Susceptibility Test Results and Clinical/Bacteriological Outcomes**

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had previously received clarithromycin/MIC ≤ 0.25 μg/mL were eradicated of H. pylori by 12 weeks (18/157) treated omeprazole. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment H. pylori isolates with amoxicillin-resistant MICs. Eleven of the patients who failed triple therapy also had post-treatment H. pylori isolates with clarithromycin-resistant MICs.

**Susceptibility Test for Neisseria gonorrhoeae**

Susceptibility test results for Neisseria gonorrhoeae are not available.

Clarithromycin MIC (μg/mL) interpretation:

- ≤ 0.25: Susceptible
- > 0.25: Intermediate
- > 1: Resistant

**Pharmacology**

- Amoxicillin is a beta-lactam antibiotic with a broad spectrum of activity against a wide range of pathogens.
- Clarithromycin is a macrolide antibiotic that inhibits bacterial protein synthesis.

**CONTRAINDICATIONS**

- Amoxicillin is contraindicated in patients with a history of severe reaction to any of the penicillins. (Refer to full prescribing information for amoxicillin before prescribing.)

**WARNINGS**

- Clarithromycin should not be used in pregnant women except in certain clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of this potential hazard to the fetus. (See WARNINGS in prescribing information for clarithromycin.)

**Amoxicillin**

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions may occur in patients treated with amoxicillin. In clinical trials, patients treated with amoxicillin reported reactions such as rash, urticaria, angioedema, and anaphylaxis. Administration of amoxicillin to patients with a history of asthma or other atopy may also increase the risk of anaphylactic reactions. Patients with a history of penicillin allergy should receive amoxicillin with caution. Cross-sensitivity to penicillins and cephalosporins may occur.

**Antimicrobials**

- Amoxicillin is effective against a wide range of bacterial pathogens, including gram-positive and gram-negative cocci and aerobes.
- Clarithromycin is effective against gram-positive and gram-negative aerobic and anaerobic bacteria, as well as Mycoplasma and Ureaplasma species.

**Precautions**

- Use with caution in patients with a history of antimicrobial therapy-associated diarrhea or pseudomembranous colitis.
- Patients with a history of allergic reactions to penicillins or cephalosporins may experience reactions to amoxicillin.

**Drug Interactions**

- Amoxicillin may interact with warfarin, increasing the risk of bleeding.
- Clarithromycin can affect the metabolism of other medications, increasing the risk of toxicity.

**References**

- Amoxicillin and clarithromycin are available in various formulations including capsules, tablets, and solutions.
- For more information, refer to the prescribing information for each medication.

**National Committee for Clinical Laboratory Standards (NCCLS)**

**INTRAUTERINE STERILIZATION AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

<table>
<thead>
<tr>
<th>PROPRANOLOL (β-blocker)</th>
<th>Delayed-Release Capsules</th>
<th>and ductal ulcer disease to eradicate H. pylori</th>
</tr>
</thead>
</table>

Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY: Clinical Studies and DOSAGE AND ADMINISTRATION).

- Among patients with ductal ulcer, PROPRANOLOL with clarithromycin is more likely to be associated with the development of clarithromycin resistance. The use of omeprazole should be discontinued if positive alternative antimicrobial therapy is initiated. (See Microbiology section and the clarithromycin package insert, MICROBIOLOGY (section).)

**Geitic Ulcer**

- PROPRANOLOL Delayed-Release Capsules are indicated for short-term management (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY: Clinical Studies, Geitic Ulcer.)

**Treatment of Gastroesophageal Reflux Disease (GERD)**

- Symptomatic GERD
- PROPRANOLOL Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

**Erosive Esophagitis**

- PROPRANOLOL Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL PHARMACOLOGY: Clinical Studies.)

**CONTRAINDICATIONS**

- Amoxicillin is contraindicated in patients with a history of severe reaction to any of the penicillins. (Refer to full prescribing information for amoxicillin before prescribing.)

**WARNINGS**

- Clostridium difficile-associated diarrhea is a common complication in patients with antibiotic use.
- Patients with a history of antibiotic-associated diarrhea should receive amoxicillin with caution.

**Drug Interactions**

- Amoxicillin and clostridium difficile-associated diarrhea are contraindicated in patients treated with amoxicillin. (See also CLINICAL PHARMACOLOGY: Pharmacokinetics.)

**CONTRAINDICATIONS**

- Clarithromycin is contraindicated in patients with a history of severe reaction to any of the penicillins. (Refer to full prescribing information for clarithromycin before prescribing.)

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

- In vitro and in vivo studies have shown that amoxicillin is not carcinogenic.
- No studies have been conducted to evaluate the effects of amoxicillin on human fertility.

**PRECAUTIONS**

- Use with caution in patients with a history of antimicrobial therapy-associated diarrhea or pseudomembranous colitis.
- Patients with a history of allergic reactions to penicillins or cephalosporins may experience reactions to amoxicillin.

**Drug Interactions**

- Amoxicillin may interact with warfarin, increasing the risk of bleeding.
- Clarithromycin can affect the metabolism of other medications, increasing the risk of toxicity.

**References**

- Amoxicillin and clarithromycin are available in various formulations including capsules, tablets, and solutions.
- For more information, refer to the prescribing information for each medication.

**National Committee for Clinical Laboratory Standards (NCCLS)**

**INTRAUTERINE STERILIZATION AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

<table>
<thead>
<tr>
<th>PROPRANOLOL (β-blocker)</th>
<th>Delayed-Release Capsules</th>
<th>and ductal ulcer disease to eradicate H. pylori</th>
</tr>
</thead>
</table>

Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY: Clinical Studies and DOSAGE AND ADMINISTRATION).

- Among patients with ductal ulcer, PROPRANOLOL with clarithromycin is more likely to be associated with the development of clarithromycin resistance. The use of omeprazole should be discontinued if positive alternative antimicrobial therapy is initiated. (See Microbiology section and the clarithromycin package insert, MICROBIOLOGY (section).)

**Geitic Ulcer**

- PROPRANOLOL Delayed-Release Capsules are indicated for short-term management (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY: Clinical Studies, Geitic Ulcer.)

**Treatment of Gastroesophageal Reflux Disease (GERD)**

- Symptomatic GERD
- PROPRANOLOL Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

**Erosive Esophagitis**

- PROPRANOLOL Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL PHARMACOLOGY: Clinical Studies.)

**CONTRAINDICATIONS**

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**WARNINGS**

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</table>
Prolinc: (enameprazole) Delayed-Release Capsules

Pregnancy

Omeprazole

Pregnancy Category C

Teratological studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence of a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 16.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryofetal toxicity and fetal skeletal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 130.8 mg/kg/day (approximately 35 to 345 times the human dose) or in animals from well-controlled studies in pregnant women. Sprague reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Clarithromycin

Pregnancy Category C

See WARNINGS (above) and full prescribing information for information for clarithromycin before using in pregnant women.

Nursing Mothers

It is not known whether omeprazole is excreted in human milk in rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 130.8 mg/kg/day (35 to 345 times the human dose) resulted in decreased body weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole and because of the potential for tumorigenicity of human milk, it is advisable not to nurse while on treatment. The decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

PRILIOSE Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3906 patients.

In the U.S. clinical trial population of 465 patients (excluding duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients treated with PRILIOSE. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as probably, possibly or definitely related to the drug:

Omeprazole (n = 465) Placbio (n = 136)

Incidence of Adverse Experiences >1%

Causal Relationship Not Assessed

Placbio (n = 120)

Body as a Whole: 5.2 Body as a Whole: 3.3

Abdominal pain 3.2 Abdominal pain 3.3

Nausea 2.9 Nausea 3.4

Vomiting 2.1 Vomiting 2.2

Dizziness 1.9 Dizziness 1.5

Diabetes 1.5 Diabetes 1.5

Atrial fibrillation 1.5 Atrial fibrillation 1.5

Cough 1.4 Cough 1.4

Anorexia 1.3 Anorexia 1.3

Atrial systolic palpitations 1.2 Atrial systolic palpitations 1.2

Back pain 1.2 Back pain 1.2

Abdominal pain unspecified 1.1 Abdominal pain unspecified 1.1

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials or occurring since the drug was marketed. These adverse experiences are divided into those which are known to be caused by a number of factors, and those which are not considered to be drug-related or the relationship to PRILIOSE was unclear.

Body as a Whole: Allergic reactions, including rash, angioedema (see also cutaneous), fever, malaise and anaphylactic shock (rare); Cardiovascular: Cough or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema.

OSDOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended oral dose of PRILIOSE is 20 mg once daily. Patients treated for an average of 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILIOSE 20 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy an additional 18 days of PRILIOSE 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (PRILIOSE/clostridinum)- The recommended adult oral regimen is PRILIOSE 40 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy an additional 18 days of PRILIOSE 20 mg once daily is recommended for ulcer healing and symptom relief.

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNING and for information regarding elderly patients. PRILIOSE in elderly is recommended for more than 5 years.

Maintenance of Healing of Eradicated H. pylori

The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastroesophageal and INDICATIONS AND USAGE. Gastro Usar)

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no histological changes is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for up to 4 weeks. (See INDICATIONS AND USAGE. Gastro Usar)

Pathological Hypersecretory Conditions

The dosage of PRILIOSE in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 10 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of more than 80 mg should be administered as divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILIOSE for more than 5 years.

No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.

PRILIOSE Delayed Release Capsules should be taken before eating. In the patients, all adverse effects of PRILIOSE. Patients should be cautioned that the PRILIOSE Delayed Release Capsule should not be chewed or crushed and should be swallowed whole.

HOW SUPPLIED

Tablet PRILIOSE Delayed-Release Capsules. 10 mg are opaque, hard gelatin, aspirin and amphetamine colored tablets, coded 606 in cap and PRILIOSE 10 on the body. They are supplied as follows:

NDC 018-066-000-11 unit of use bottles of 30

NDC 018-066-66-00 unit of use bottles of 40

NDC 018-066-66-08 unit of use bottles of 100

NDC 018-066-66-10 unit of use bottles of 200

PRILIOSE Delayed-Release Capsules, 20 mg are opaque, hard gelatin, asoxphan and amphetamine colored capsules, coded 747 on cap and PRILIOSE 20 on the body. They are supplied as follows:

NDC 018-067-22-02 unit of use bottles of 30

NDC 018-067-22-31 unit of use bottles of 300

NDC 018-067-22-32 unit of use bottles of 100

NDC 018-067-22-67 unit of use bottles of 100

NDC 018-067-22-68 unit of use bottles of 200

NDC 018-067-22-69 unit of use bottles of 200

NDC 018-067-23-00 unit of use bottles of 100

NDC 018-067-23-06 unit of use bottles of 100

NDC 018-067-23-08 unit of use bottles of 200

NDC 018-067-23-20 unit of use bottles of 200

NDC 018-067-23-31 unit of use bottles of 300

Storage

Store PRILIOSE Delayed-Release Capsules in a light-resistant container protected from light and moisture. Store between 15° and 30°C (59°F and 86°F).
(Nos. 1541, 3046)

Ref. 03-4953-R13-Rev. May, 1999

**PREVACID**

(pré va-sid)

(lansoprazole)

Delayed-Release Capsules

**DESCRIPTION**

The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a substituted benzimidazole, 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfanyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $\text{C}_{19}\text{H}_{14}\text{F}_{3}\text{N}_{3}\text{O}_{2}\text{S}$ with a molecular weight of 369.37. The structural formula is:

![Structural Formula](attachment:image)

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the $t_{1/2}$ is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide. D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

* PREVACID 15-mg capsules only.
CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism
PREVACID Delayed-Release Capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (Cmax) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption
The absorption of lansoprazole is rapid, with mean Cmax occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (± SD) plasma half-life was 1.5 (± 1.0) hours. Both Cmax and AUC are diminished by about 50% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution
Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 μg/mL.

Metabolism
Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H+K+)-ATPase within the parietal cell canalculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours.

Elimination
Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radioactivity was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Geriatric
The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Pediatric
The pharmacokinetics of lansoprazole has not been investigated in patients <18 years of age.

Gender
In a study comparing 12 male and six female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results. (Also see Use in Women.)

Renal Insufficiency
In patients with severe renal insufficiency, plasma protein binding decreased by 1.0%-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and Cmax and Tmax were not different from subjects with healthy kidneys.
Hepatic Insufficiency
In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race
The pooled mean pharmacokinetic parameters of lansoprazole from twelve U.S. Phase 1 studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The Cmax values were comparable.

PHarmacodynamics
Mechanism of action
Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H+K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory activity
After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study comparing lansoprazole 15 and 30 mg with omeprazole 20 mg for five days, the following effects on intragastric pH were noted:

**Mean Antisecretory Effects after Single and Multiple Daily Dosing**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Value</th>
<th>PREVACID 15 mg</th>
<th>Omeprazole 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24 Hour pH</td>
<td>21</td>
<td>2.7*</td>
<td>4.0*</td>
</tr>
<tr>
<td>Mean Nighttime pH</td>
<td>12</td>
<td>2.4</td>
<td>3.0*</td>
</tr>
<tr>
<td>% Time Gastric pH&lt;3</td>
<td>18</td>
<td>33*</td>
<td>59*</td>
</tr>
<tr>
<td>% Time Gastric pH&lt;4</td>
<td>12</td>
<td>22*</td>
<td>49*</td>
</tr>
</tbody>
</table>

*Note: An intragastric pH of 4 reflects a reduction in gastric acid by 99%
1: p<0.05 versus baseline, 2: lansoprazole 15 mg and omeprazole 20 mg
2: p<0.05 versus baseline only

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg, 2-3 hours with lansoprazole 15 mg, and 3-4 hours with omeprazole 20 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori* (H. pylori). The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID given q.d., b.i.d. and t.i.d.
Mean Antisecretory Effects After 5 Days of b.i.d. and t.i.d. Dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30 mg q.d</th>
<th>15 mg b.i.d</th>
<th>30 mg b.i.d</th>
<th>30 mg t.i.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Time Gastric pH&lt;5</td>
<td>43</td>
<td>47</td>
<td>59</td>
<td>77</td>
</tr>
<tr>
<td>% Time Gastric pH&gt;6</td>
<td>20</td>
<td>23</td>
<td>28</td>
<td>45</td>
</tr>
</tbody>
</table>

(15 mg q.d. was PREVACID 15 mg and 30 mg q.d. was PREVACID 30 mg)

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over two to four days after multiple doses. There is no indication of rebound gastric acidity.

**Enterochromaffin-like (ECL) cell effects**

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. (See **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**.)

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

**Other gastric effects in humans**

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

**Serum gastrin effects**

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with lansoprazole given orally in doses of 15 mg to 60 mg. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

**Endocrine effects**

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates.

**Other effects**

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after
lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

CLINICAL PHARMACOLOGY
MICROBIOLOGY

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

**Helicobacter**
*Helicobacter pylori*

**Pretreatment Resistance**
Clarithromycin pretreatment resistance (≥ 2.0 μg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 μg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of > 0.25 μg/mL. One patient on the 14-day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 μg/mL by E-test and the patient was eradicated of *H. pylori*.

### Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

<table>
<thead>
<tr>
<th>Clarithromycin Pretreatment Results</th>
<th>H. pylori negative – not eradicated</th>
<th>H. pylori positive – not eradicated</th>
<th>Post-treatment susceptibility results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP</td>
<td>p</td>
<td>R</td>
</tr>
<tr>
<td>Triple Therapy 14-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399 M95-131 M95-392)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>112</td>
<td>105</td>
<td>7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Resistant</td>
<td>17</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
</table>

| Triple Therapy 10-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399) |
| Suspceptible                      | 42 | 40 |
| Intermediate                      | 1 | 1 |
| Resistant                         | 4 | 1 | 3 |

---

* Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

**Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤ 0.25 μg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of > 0.25 μg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the
patients failed lansoprazole 30 mg t.i.d./amoxicillin 1 gm t.i.d. dual therapy and a total of 12.8% (22/172) of the patients failed the 10- and 14-day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

**Susceptibility Test for *Helicobacter pylori***
The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1 x 10^7 - 1 x 10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>Clarithromycin MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.5 - 1.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>Resistant (R)</td>
</tr>
<tr>
<td>Amoxicillin MIC (µg/mL)</td>
<td>Interpretation</td>
</tr>
<tr>
<td>≤ 0.25</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

*These are guideline breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.*

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antimicrobial Agent</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> ATCC 43504</td>
<td>Clarithromycin</td>
<td>0.015 - 0.12 mg/mL</td>
</tr>
<tr>
<td><em>H. pylori</em> ATCC 43504</td>
<td>Amoxicillin</td>
<td>0.015 - 0.12 mg/mL</td>
</tr>
</tbody>
</table>

*These are quality control ranges for the agar dilution methodology and they should not be used to control results obtained using alternative methods.*

**Reference**


**CLINICAL STUDIES**

**Duodenal Ulcer**

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, or 60 mg of PREVACID once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with PREVACID 15 mg. Based on this study and the second study described below, the recommended dose of PREVACID in duodenal ulcer is 15 mg per day.

**Duodenal Ulcer Healing Rates**

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http://www.prevacid.com/pro/comppi.cfm

8/29/00
PREVACID 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo-controlled, dose-comparison (15 and 30 mg of PREVACID once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the higher dose of PREVACID. Although the 15-mg dose of PREVACID was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of PREVACID and ranitidine leaves the comparative effectiveness of the two agents undetermined.

**Duodenal Ulcer Healing Rates**

<table>
<thead>
<tr>
<th></th>
<th>PREVACID 15 mg q.d</th>
<th>PREVACID 30 mg q.d</th>
<th>Ranitidine 300 mg h.s.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>(N=60)</td>
<td>(N=71)</td>
<td>(N=62)</td>
<td>(N=41)</td>
</tr>
<tr>
<td>2</td>
<td>42.4%</td>
<td>45.5%</td>
<td>46.7%</td>
<td>38.3%</td>
</tr>
<tr>
<td>4</td>
<td>67.4%</td>
<td>69.2%</td>
<td>69.9%</td>
<td>63.1%</td>
</tr>
</tbody>
</table>

*p<0.05* versus placebo

**H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of PREVACID in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy or in combination with amoxicillin capsules as dual 14-day therapy for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

- **Triple therapy**: PREVACID 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.
- **Dual therapy**: PREVACID 30 mg t.i.d./amoxicillin 1 gm t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4-6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of PREVACID triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori*.

**H. pylori Eradication Rates – Triple Therapy**

(PREVACID/amoxicillin/clarithromycin)

Percent of Patients Cured

[95% Confidence Interval]

(Number of patients)

http://www.prevacid.com/oro/compoi.cfm
H. pylori Eradication Rates – 14-Day Dual Therapy
(PREVACID/amoxicillin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dual Therapy Evaluable Analysis*</th>
<th>Dual Therapy Intent-to-Treat Analysis#</th>
</tr>
</thead>
<tbody>
<tr>
<td>M93-131</td>
<td>77 T</td>
<td>70 T</td>
</tr>
<tr>
<td>(62.5 – 84.2)</td>
<td>(56.8 – 81.2)</td>
<td></td>
</tr>
<tr>
<td>(N=51)</td>
<td>(N=60)</td>
<td></td>
</tr>
<tr>
<td>M93-125</td>
<td>66 T</td>
<td>61 T</td>
</tr>
<tr>
<td>(51.9 – 77.5)</td>
<td>(48.5 – 72.9)</td>
<td></td>
</tr>
<tr>
<td>(N=58)</td>
<td>(N=67)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on evaluable patients with confirmed H. pylori infection at baseline and at least one post-baseline test- of- cure with at least 50% reduction in either urea breath test, IgG antibody test, or culture. Patients were excluded from the analysis if they completed the study. Additionally, patients dropped out of the study due to an adverse event related to the study drug. They were included in the evaluable analysis as failures of therapy.

# (p<0.05) versus PREVACID alone

Long-Term Maintenance Treatment of Duodenal Ulcers
PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

Endoscopic Remission Rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>No. of Pts</th>
<th>0-3 mo.</th>
<th>0-6 mo.</th>
<th>0-12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>PREVACID 15 mg q d</td>
<td>86</td>
<td>90%*</td>
<td>87%*</td>
<td>84%*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>83</td>
<td>49%</td>
<td>41%</td>
<td>39%</td>
</tr>
<tr>
<td>#2</td>
<td>PREVACID 30 mg q d</td>
<td>18</td>
<td>94%*</td>
<td>94%*</td>
<td>85%*</td>
</tr>
<tr>
<td></td>
<td>PREVACID 15 mg q d</td>
<td>15</td>
<td>87%*</td>
<td>79%*</td>
<td>70%*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>15</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* p < 0.05 vs Placebo
In trial #2, no significant difference was noted between PREVACID 15 mg and 30 mg in maintaining remission.

**Gastric Ulcer**

In a U.S. multicenter, double-blind, placebo-controlled study of 253 patients with endoscopically documented gastric ulcer, the percentage of patients healed at four and eight weeks was significantly higher with PREVACID 15 mg and 30 mg once a day than with placebo.

**Gastric Ulcer Healing Rates**

<table>
<thead>
<tr>
<th>Week</th>
<th>PREVACID 15 mg (n=65)</th>
<th>PREVACID 30 mg (n=65)</th>
<th>Placebo (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>54.8%</td>
<td>58.1%</td>
<td>53.3%</td>
</tr>
<tr>
<td>8</td>
<td>92.3%</td>
<td>96.8%</td>
<td>93.2%</td>
</tr>
</tbody>
</table>

* p<0.05 vs. placebo

Patients treated with any PREVACID dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than the placebo group. Independent substantiation of the effectiveness of PREVACID 30 mg was provided by a meta-analysis of published and unpublished data.

**Gastroesophageal Reflux Disease (GERD)**

**Symptomatic GERD**

In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=48)</th>
<th>PREVACID 15 mg (n=80)</th>
<th>PREVACID 30 mg (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Days without Heartburn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>0%</td>
<td>71%</td>
<td>46%</td>
</tr>
<tr>
<td>Week 4</td>
<td>11%</td>
<td>81%</td>
<td>76%</td>
</tr>
<tr>
<td>Week 8</td>
<td>13%</td>
<td>84%</td>
<td>82%</td>
</tr>
<tr>
<td>% of Nights without Heartburn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>13%</td>
<td>86%</td>
<td>57%</td>
</tr>
<tr>
<td>Week 4</td>
<td>25%</td>
<td>89%</td>
<td>73%</td>
</tr>
<tr>
<td>Week 8</td>
<td>36%</td>
<td>92%</td>
<td>80%</td>
</tr>
</tbody>
</table>

* p<0.01 vs. placebo

**Mean Severity of Day Heartburn By Study Day For Evaluation Patients**

(3=Severe, 2=Moderate, 1=Mild, 0=None)

---

http://www.prevacid.com/pro/command.cfm

8/29/00
In two U.S., multicenter double-blind, ranitidine-controlled studies of 925 total patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, lansoprazole 15 mg was superior to ranitidine 150 mg (BID) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8 week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed.

**Erosive Esophagitis**

In a U.S. multicenter, double-blind, placebo-controlled study of 269 patients entering with an endoscopic diagnosis of esophagitis with mucosal grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing were as follows:

**Erosive Esophagitis Healing Rates**

<table>
<thead>
<tr>
<th>Week</th>
<th>PREVACID 15 mg q.d.</th>
<th>PREVACID 30 mg q.d.</th>
<th>PREVACID 60 mg q.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>67.6%***</td>
<td>81.3%***</td>
<td>89.6%***</td>
<td>32.8%</td>
</tr>
<tr>
<td>5</td>
<td>87.7%***</td>
<td>95.4%***</td>
<td>94.3%</td>
<td>52.5%</td>
</tr>
<tr>
<td>8</td>
<td>90.9%***</td>
<td>95.4%***</td>
<td>94.4%</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

* p<0.01 vs. placebo  
** p<0.05 vs. PREVACID 15 mg and placebo

In this study, all PREVACID groups reported significantly greater relief of heartburn and less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets taken per day than the placebo group.

Although all doses were effective, the earlier healing in the higher two doses suggests 30 mg q.d. as the recommended dose.

PREVACID was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. PREVACID at a dose of 30 mg was significantly more effective than ranitidine 150 mg b.i.d. as shown below.

**Erosive Esophagitis Healing Rates**
In addition, patients treated with PREVACID reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg b.i.d.

Although this study demonstrates effectiveness of PREVACID in healing erosive esophagitis, it does not represent an adequate comparison with ranitidine because the recommended ranitidine dose for esophagitis is 150 mg q.i.d., twice the dose used in this study.

In the two trials described and in several smaller studies involving patients with moderate to severe erosive esophagitis, PREVACID produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg b.i.d. in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H₂-receptor antagonist given at the dose indicated for symptom relief or greater, namely, cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg b.i.d. in healing reflux esophagitis, and the percentage of patients with healing were as follows. This study does not constitute a comparison of the effectiveness of histamine H₂-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H₂-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H₂-receptor antagonist.

### Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H₂-Receptor Antagonist Therapy

<table>
<thead>
<tr>
<th>Week</th>
<th>PREVACID 30 mg q.d.</th>
<th>Ranitidine 150 mg b.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>74.7%*</td>
<td>42.8%</td>
</tr>
<tr>
<td>8</td>
<td>83.7%*</td>
<td>32.0%</td>
</tr>
</tbody>
</table>

* p<0.001 versus ranitidine

### Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed esophagitis. Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period.

### Endoscopic Remission Rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>No. of Ps</th>
<th>0-3 mo</th>
<th>0-6 mo</th>
<th>0-12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>PREVACID 15 mg q.d.</td>
<td>59</td>
<td>83%*</td>
<td>81%*</td>
<td>79%*</td>
</tr>
<tr>
<td></td>
<td>PREVACID 30 mg q.d.</td>
<td>56</td>
<td>93%*</td>
<td>93%*</td>
<td>90%*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>55</td>
<td>31%</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>#2</td>
<td>PREVACID 15 mg q.d.</td>
<td>50</td>
<td>74%*</td>
<td>72%*</td>
<td>67%*</td>
</tr>
<tr>
<td></td>
<td>PREVACID 30 mg q.d.</td>
<td>49</td>
<td>75%*</td>
<td>72%*</td>
<td>55%*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>16%</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* p<0.001 versus placebo
Regardless of initial grade of erosive esophagitis, PREVACID 15 mg and 30 mg were similar in maintaining remission.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients. (See DOSAGE AND ADMINISTRATION.) PREVACID was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZE patients, serum gastrin levels were not modified by PREVACID. However, in some patients, serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

INDICATIONS AND USAGE

Short-Term Treatment of Active Duodenal Ulcer
PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy (PREVACID/amoxicillin/clarithromycin)
PREVACID Delayed-Release Capsules, in combination with amoxicillin plus clarithromycin as triple therapy, are indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual Therapy (PREVACID/amoxicillin)
PREVACID Delayed-Release Capsules, in combination with amoxicillin as dual therapy, are indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected. (See the clarithromycin package insert, MICROBIOLOGY section.) Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Maintenance of Healed Duodenal Ulcers
PREVACID Delayed-Release Capsules are indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer
PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
PREVACID Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis
PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.
For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment.

If there is a recurrence of erosive esophagitis an additional 8-week course of PREVACID may be considered.

**Maintenance of Healing of Erosive Esophagitis**
PREVACID Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

**Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**
PREVACID Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

**CONTRAINDICATIONS**
PREVACID Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin before prescribing.)

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic, and in patients receiving terfenadine therapy who have preexisting cardiac abnormalities or electrolyte disturbances. (Please refer to full prescribing information for clarithromycin before prescribing.)

**WARNINGS**
CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (SEE WARNINGS IN PRESCRIBING INFORMATION FOR CLARITHROMYCIN.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.
There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General
Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients
PREVACID Delayed-Release Capsules should be taken before eating.

Alternative Administration Options
For patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened, and the intact granules contained within can be sprinkled on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt, or strained pears and swallowed immediately. The granules should not be chewed or crushed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL – approximately 2 ounces), mixed briefly and swallowed immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. The granules have also been shown in vitro to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be opened and the intact granules mixed in 40 mL of apple juice and injected through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional apple juice to clear the tube.

Drug Interactions
Lansoprazole is metabolized through the cytochrome P<sub>450</sub> system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P<sub>450</sub> system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P<sub>450</sub> isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release.
Capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50-kg person of average height (1.46 m² body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m²). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in in vitro human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy: Teratogenic Effects. Pregnancy Category B
Lansoprazole
Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clarithromycin
Pregnancy Category C
SeeWARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers
Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the

http://www.prevacid.com/pro/comppi.cfm
mother.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Use in Women**
Over 800 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

**Use in Geriatric Patients**
Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

**ADVERSE REACTIONS**

Worldwide, over 6100 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in PREVACID-treated patients than placebo-treated patients:

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>PREVACID (N=1457) %</th>
<th>Placebo (N=467) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 mg and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system.

- **Body as a Whole** - anaphylactoid-like reaction, asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise; **Cardiovascular System** - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; **Digestive System** - melena, anorexia, bezoar, cardiomyopathy, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis, vomiting; **Endocrine System** - diabetes mellitus, goiter, hyperglycemia/hypoglycemia; **Hematologic and Lymphatic System** - agranulocytosis, anemia, aplastic anemia, hemolysis, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia,
and thrombotic thrombocytopenic purpura; Metabolic and Nutritional Disorders - gout, weight gain/loss; Musculoskeletal System - arthritis/arthritis, musculoskeletal pain, myalgia; Nervous System - agitation, amnesia, anxiety, apathy, confusion, depression, dizziness/syncope, hallucinations, hemiplegia, hostility aggravated, libido decreased, nervousness, paresthesia, thinking abnormality; Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccups, pneumonia, upper respiratory inflammation/infection; Skin and Appendages - acne, alopecia, pruritus, rash, urticaria; Special Senses - blurred vision, deafness, eye pain, visual field defect, otitis media, speech disorder, taste perversion, tinnitus; Urogenital System - abnormal menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus, urinary retention.

*The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.

Combination Therapy with Amoxicillin and Clarithromycin
In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID, amoxicillin, or clarithromycin.

Triple Therapy: PREVACID/amoxicillin/clarithromycin
The most frequently reported adverse events for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: PREVACID/amoxicillin
The most frequently reported adverse events for patients who received PREVACID t.i.d. plus amoxicillin t.i.d. dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with PREVACID t.i.d. plus amoxicillin t.i.d. dual therapy than with PREVACID alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, ADVERSE REACTIONS sections.

Laboratory Values
The following changes in laboratory parameters for lansoprazole were reported as adverse events:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (1/250) placebo patients and 0.3% (2/795) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory value changes with amoxicillin or clarithromycin, refer to their package inserts, ADVERSE REACTIONS section.
OVERDOSAGE
Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Duodenal Ulcer
The recommended adult oral dose is 15 mg once daily for 4 weeks. (See INDICATIONS AND USAGE.)

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy: PREVACID/amoxicillin/clarithromycin
The recommended adult oral dose is 30 mg PREVACID, 1 gram amoxicillin, and 500 mg clarithromycin, all given twice daily (q 12h) for 10 or 14 days. (See INDICATIONS AND USAGE.)

Dual Therapy: PREVACID/amoxicillin
The recommended adult oral dose is 30 mg PREVACID and 1 gram amoxicillin, each given three times daily (q 8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally-impaired patients.

Maintenance of Healed Duodenal Ulcers
The recommended adult oral dose is 15 mg once daily. (See CLINICAL STUDIES.)

Short-Term Treatment of Gastric Ulcer
The recommended adult oral dose is 30 mg once daily for up to eight weeks. (See CLINICAL STUDIES.)

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
The recommended adult oral dose is 15 mg once daily for up to 8 weeks.

Short-Term Treatment of Erosive Esophagitis
The recommended adult oral dose is 30 mg once daily for up to 8 weeks. For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. (See INDICATIONS AND USAGE.)

If there is a recurrence of erosive esophagitis, an additional 8-week course of PREVACID may be considered.

Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is 15 mg once daily. (See CLINICAL STUDIES.)

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of PREVACID in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg b.i.d. have been administered. Daily dosages of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PREVACID for more
than four years.

No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

PREVACID Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PREVACID.

**Alternative Administration Options**

For patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened, and the intact granules contained within can be sprinkled on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt, or strained pears and swallowed immediately. The granules should not be chewed or crushed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL – approximately 2 ounces), mixed briefly and swallowed immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. The granules have also been shown *in vitro* to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be opened and the intact granules mixed in 40 mL of apple juice and injected through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional apple juice to clear the tube.

**HOW SUPPLIED**

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green with the TAP logo and "PREVACID 15" imprinted on the capsules. The 30 mg are opaque, hard gelatin, colored pink and black with the TAP logo and "PREVACID 30" imprinted on the capsules. They are available as follows:

- **NDC 0300-1541-30** Unit of use bottles of 30: 15-mg capsules
- **NDC 0300-1541-13 Bottles of 100: 15-mg capsules**
- **NDC 0300-1541-19 Bottles of 1000: 15-mg capsules**
- **NDC 0300-1541-11 Unit dose package of 100: 15-mg capsules**
- **NDC 0300-3046-13 Bottles of 100: 30-mg capsules**
- **NDC 0300-3046-19 Bottles of 1000: 30-mg capsules**
- **NDC 0300-3046-11 Unit dose package of 100: 30-mg capsules**

Storage: PREVACID capsules should be stored in a tight container protected from moisture.

Store between 15°C and 30°C (59°F and 86°F).

**Rx only**

U.S. Patent Nos. 4,628,098; 4,689,333; 5,013,743; 5,026,560 and 5,045,321.

**Manufactured for**
TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.
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Osaka, Japan 541

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