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

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
September 21, 2000	September 29, 2000	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:	MANUFACTURER:
Nexium (Esomeprazole Magnesium Delayed-Release Tablets) 20 mg and 40 mg **NDA #: 21-153**	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/ 9/28/2000
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/ 10/2/00
Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-400 (OPDRA); Attention: Jerry Phillips; Parklawn Bldg. Rm. 15B03			FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products)	
DATE: July 11, 2000	IND NO.:	NDA NO.: 21-153	TYPE OF DOCUMENT: Labeling	DATE OF DOCUMENT: 4/3/00 and 12/3/99
NAME OF DRUG: Nexium (esopmeprazole magnesium) Delayed-Release Capsules	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG: 2S	DESIRED COMPLETION DATE: 9/4/00

NAME OF FIRM: AstraZeneca LP

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Proprietary tradename - follow-up review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a follow-up consult request for evaluation of the proprietary tradename: Nexium (esomperazole 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).

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

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND

SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

APPEARS THIS WAY
ON ORIGINAL

NOV 29 1999

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)

IND#: ——

MANUFACTURER: AstraZeneca LP

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 30 1999
HFD-180

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/ 11/29/99

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

/S/ 11/29/99

Peter 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 Wa[illegible]
2/15/01 [illegible]
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 /S/ 21.164

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

SUBJECT: **Final Revised Draft Labeling**
NDA 21-153, Nexium (esopmeprazole 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

MEMORANDUM

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

DATE: January 31, 2001

TO: NDA 21-153 and NDA 21-154 /S/ 1/31/01

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 duodeanl 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 6

Draft

Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-153

DISCIPLINE REVIEW LETTER

AstraZeneca LP
Attention: Kathyrn 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:

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

APPEARS THIS WAY
ON ORIGINAL

/s/

Liang Zhou
1/12/01 07:03:44 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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.
Regulatroy Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-153

DISCIPLINE REVIEW LETTER

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

NOV 29 2000

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:

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-153

NOV 15

AstraZeneca LP
Attention: Kathyrn 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

Walsh

NDA 21-153

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

OCT 26 2000

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

APPEARS THIS WAY
ON ORIGINAL

Walsh

NDA 21-153

DISCIPLINE REVIEW LETTER

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

SEP 26 2000

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

[redacted] is the S-isomer of omeprazole."

to

"Esomeprazole is the S-isomer of omeprazole."

B. Change the molecular formula from:

"$C_{34}H_{36}N_6O_6S_2Mg \times 3H_2O$"

to

"$(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$"

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/ for 9/27/02

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

WKW 8 4

NDA 21-153

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

AUG - 8 2000

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 [redacted] for DMF [redacted]

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 constued 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 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

Walsh

NDA 21-153

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 Biopharmacuetics-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

Walsh

MEMORANDUM OF TELECON

DATE: July 17, 2000

APPLICATION NUMBER: NDA 21-153; Nexium (esomeprazole magnesium) Del;ayed-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/ 7/31/00
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.Doddapaneni

filename: ——————

TELECON

APPEARS THIS WAY
ON ORIGINAL

NDA 21-153

INFORMATION REQUEST LETTER

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

MAY 25 2000

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).
   B. DMF —— amendment dated July 7, 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

JAN - 5 2000

NDA 21-153

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: _____

APPEARS THIS WAY
ON ORIGINAL

ADVICE (AD)

NDA 21-153

DEC - 8 1999

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)

APPEARS THIS WAY
ON ORIGINAL

Walsh

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)]

October 2, 2000

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Dennis S. Riff, M.D.
1211 W. La Palma Avenue, Suite 306
Anaheim, California 92801

AUG 17 2000

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Walsh

Food and Drug Administration
Rockville MD 20857

David Chua, M.D.
1 South 280 Summit Avenue
Court A-1
Oakbrook Terrace, Illinois 60181

AUG 17 2000

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Howard Schwartz, M.D.
Miami Research Associates
7500 SW 87th Avenue, Suite #200
Miami, Florida 33176

G 17 2000

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Walsh

Food and Drug Administration
Rockville MD 20857

Jeffrey R. Breiter, M.D.
945 Main Street, Suite 202-203
Manchester, Connecticut 06040

JUL 25 2000

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

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

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.

1. "CLINICAL PHARMACOLOGY" "Enterochromaffin-like (ECL) cell Effects"- on Sponsor's page 9.

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

Jasti B. Choudary, B.V.Sc., Ph.D.

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

/s/

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

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: September 15, 2000

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

Subject: NDA 21,153 (Nexium/esomeprazole magnesium, Delayed-Release Capsules). Amendment Dated August 2, 2000- Sponsor's Revised Draft Labeling.

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"

   "a. Carcinogenesis, Mutagenesis, Impairment of Fertility- on sponsor's pages 20 and 21.

   b. "Pregnancy•Teratogenic Effects•Pregnancy Category B." – On sponsor's pages 21_22.

   c. "Nursing Mothers" on sponsor's page 23.

[ ]

WITHHOLD 5 PAGES

Draft

Labeling

[ ]

/S/ 9/18/00

Jasti B. Choudary, B.V.Sc, Ph.D.

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

NDA Number:	021153	**Trade Name:**	NEXIUM 20/40MG DELAYED RELEASE CAPSULES
Supplement Number:	000	**Generic Name:**	NEXIUM 20/40MG DELAYED RELEASE CAPSULES
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	TREATMENT OF EROSIVE ESOPHAGITIS/HEALING/MAINTENANCE/SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE
Action Date:	10/3/00		

Indication # 1 Healing of erosive esophagitis
Label Adequacy: Inadequate for ALL pediatric age groups
Formulation Needed:
Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	2 years	Deferred	
2 years	16 years	Deferred	2/20/01

Indication # 2 Maintenance of healing of erosive esophagitis
Label Adequacy: Inadequate for ALL pediatric age groups
Formulation Needed:
Comments (if any):

Lower Range	Upper Range	Status	Date

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):

Lower Range	Upper Range	Status	Date

This page was last edited on 2/15/01

Maria Walsh
Signature

2/15/01
Date

Other Labeling In Class:

Prilosec (omeprazole)

Prevacid (lansoprazole)

Prilosec®

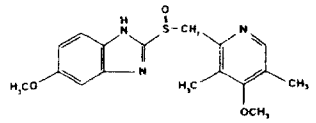
9194131
64000431

(omeprazole)

DELAYED-RELEASE CAPSULES

DESCRIPTION

The active ingredient in PRILOSEC* (omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



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 acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

PRILOSEC is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C Blue #2, D&C Red #7 Calcium Lake, and, in addition, the 10 mg and 40 mg capsule shells also contain D&C Yellow #10.

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 absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%.

The bioavailability of omeprazole increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Pharmacokinetics: Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin: the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations
2 hours after Dose[1]

Tissue	Clarithromycin	Clarithromycin+ Omeprazole
Antrum	10.48 ± 2.01 (n = 5)	19.96 ± 4.71 (n = 5)
Fundus	20.81 ± 7.64 (n = 5)	24.25 ± 6.37 (n = 5)
Mucus	4.15 ± 7.74 (n = 4)	39.29 ± 32.79 (n = 4)

[1] Mean ± SD (µg/g)

For information on clarithromycin pharmacokinetics and microbiology, consult the clarithromycin package insert, CLINICAL PHARMACOLOGY section.

The pharmacokinetics of omeprazole, clarithromycin, and amoxicillin have not been adequately studied when all three drugs are administered concomitantly.

For information on amoxicillin pharmacokinetics and microbiology, see the amoxicillin package insert, ACTIONS, PHARMACOLOGY and MICROBIOLOGY sections.

Pharmacodynamics

Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic 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 gastric mucosa, omeprazole 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 acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2-6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies
of the Mean Antisecretory Effects of Omeprazole
After Multiple Daily Dosing

Parameter	Omeprazole 20 mg		Omeprazole 40 mg	
	Max	Min	Max	Min
% Decrease in Basal Acid Output	78*	58-80	94*	80-93
% Decrease in Peak Acid Output	79*	50-59	88*	62-68
% Decrease in 24-hr. Intragastric Acidity		80-97		92-94

*Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.)

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer— In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 99)	Placebo a.m. (n = 48)
Week 2	*41	13
Week 4	*75	27

*($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) 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 ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d (n = 148)
Week 2	42	34
Week 4	*82	63

*($p < 0.01$)

Healing occurred significantly faster in patients treated with PRILOSEC than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of PRILOSEC were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of PRILOSEC were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg (n = 34)	PRILOSEC 40 mg (n = 36)	Ranitidine 150 mg b.i.d (n = 35)
Week 2	* 83	* 83	53
Week 4	* 97	*100	82
Week 8	100	100	94

*($p \leq 0.01$)

H. pylori Eradication in Patients with Duodenal Ulcer Disease

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)— Three U.S. randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared PRILOSEC plus clarithromycin plus amoxicillin to clarithromycin plus amoxicillin. Two studies (126 and 127) were conducted in patients with an active duodenal ulcer, and the other study (M96-446) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. The dose regimen in the studies was PRILOSEC 20 mg b.i.d. plus clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days; or clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days. In studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of PRILOSEC 20 mg q.d. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest®, histology and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive.

The combination of omeprazole plus clarithromycin plus amoxicillin was effective in eradicating *H. pylori*.

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates
% of Patients Cured [95% Confidence Interval]

	PRILOSEC +clarithromycin +amoxicillin		Clarithromycin +amoxicillin	
	Per-Protocol[†]	Intent-to-Treat[‡]	Per-Protocol[†]	Intent-to-Treat[‡]
Study 126	*77 [64, 86] (n = 64)	*69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Study 127	*78 [67, 88] (n = 65)	*73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 83)
Study M96-446	*90 [80, 96] (n = 69)	*83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

[†] Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 126 and 127, history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

[‡] Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

* ($p < 0.05$) versus clarithromycin plus amoxicillin

Dual Therapy (PRILOSEC/clarithromycin)— Four randomized, double-blind, multicenter studies (M93-067, M93-100, M92-812b, and M93-058) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or by PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies M93-067 and M93-100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 228 patients in Study M93-100. These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies. Studies M92-812b and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in study M92-812b and 208 patients in Study M93-058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies 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 of *H. pylori*. In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that 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*.

H. pylori Eradication Rates (Per-Protocol Analysis at 4 to 6 Weeks)
% of Patients Cured [95% Confidence Interval]

	PRILOSEC + Clarithromycin	PRILOSEC	Clarithromycin
U.S. Studies			
Study M93-067	74 [60, 85][†‡] (n = 53)	0 [0, 7] (n = 54)	31 [18, 47] (n = 42)
Study M93-100	64 [51, 76][†‡] (n = 61)	0 [0, 6] (n = 59)	39 [24, 55] (n = 44)
Non U.S. Studies			
Study M92-812b	83 [71, 92][‡] (n = 60)	1 [0, 7] (n = 74)	N/A
Study M93-058	74 [64, 83][‡] (n = 86)	1 [0, 6] (n = 90)	N/A

[†] Statistically significantly higher than clarithromycin monotherapy ($p < 0.05$)
[‡] Statistically significantly higher than omeprazole monotherapy ($p < 0.05$)

Ulcer healing was not significantly different when clarithromycin was added to omeprazole therapy compared to omeprazole therapy alone.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori* and reduced duodenal ulcer recurrence.

Duodenal Ulcer Recurrence Rates by *H. pylori* Eradication Status
% of Patients with Ulcer Recurrence

	H. pylori eradicated[*]	*H. pylori* not eradicated[*]
U.S. Studies[†]		
6 months post-treatment		
Study M93-067	*35 (n = 49)	60 (n = 88)
Study M93-100	*8 (n = 53)	60 (n = 106)
Non U.S. Studies[‡]		
6 months post-treatment		
Study M92-812b	*5 (n = 43)	46 (n = 78)
Study M93-058	*6 (n = 53)	43 (n = 107)
12 months post-treatment		
Study M92-812b	*5 (n = 39)	68 (n = 71)

[*] *H. pylori* eradication status assessed at same timepoint as ulcer recurrence
[†] Combined results for PRILOSEC + clarithromycin, PRILOSEC, and clarithromycin treatment arms
[‡] Combined results for PRILOSEC + clarithromycin and PRILOSEC treatment arms
* ($p \leq 0.01$) versus proportion with duodenal ulcer recurrence who were not *H. pylori* eradicated

Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 202)	PRILOSEC 40 mg q.d. (n = 214)	Placebo (n = 104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**,†	48.1

** ($p < 0.01$) PRILOSEC 40 mg or 20 mg versus placebo
† ($p < 0.05$) PRILOSEC 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 200)	PRILOSEC 40 mg q.d. (n = 187)	Ranitidine 150 mg b.i.d. (n = 199)
Week 4	63.5	78.1**,††	56.3
Week 8	81.5	91.4**,††	78.4

** ($p < 0.01$) PRILOSEC 40 mg versus ranitidine
†† ($p < 0.01$) PRILOSEC 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[*]

	PRILOSEC 20 mg a.m.	PRILOSEC 10 mg a.m.	Placebo a.m.
All patients	46*,† (n = 205)	31† (n = 199)	13 (n = 105)
Patients with confirmed GERD	56*,† (n = 115)	36† (n = 109)	14 (n = 59)

[*] Defined as complete resolution of heartburn
* ($p < 0.005$) versus 10 mg
† ($p < 0.005$) versus placebo

Erosive Esophagitis

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of PRILOSEC Delayed-Release Capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg PRILOSEC (n = 83)	40 mg PRILOSEC (n = 87)	Placebo (n = 43)
4	39**	45**	7
8	74**	75**	14

** ($p < 0.01$) PRILOSEC versus placebo.

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 comparisons with histamine H_2-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 controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with PRILOSEC than in those taking placebo or histamine H_2-receptor antagonists.

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

Long Term Maintenance Treatment of Erosive Esophagitis

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

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 138)	PRILOSEC 20 mg 3 days per week (n = 137)	Placebo (n = 131)
Percent in endoscopic remission at 6 months	*70	34	11

* ($p < 0.01$) PRILOSEC 20 mg q.d. versus PRILOSEC 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, PRILOSEC 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 131)	PRILOSEC 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	*77	†58	46

* ($p = 0.01$) PRILOSEC 20 mg q.d. versus PRILOSEC 10 mg q.d. or Ranitidine.
† ($p = 0.03$) PRILOSEC 10 mg q.d. versus Ranitidine.

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 effectiveness.

Pathological Hypersecretory Conditions

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 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). PRILOSEC was well tolerated at these high dose levels for prolonged periods (> 5 years in some patients). In most ZE 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 tumors, 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

Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). 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 (126, 127, M96-446). 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 unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest®.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]						
Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative - eradicated	*H. pylori* positive - not eradicated			
			Post-treatment susceptibility results			
			S[b]	I[b]	R[b]	No MIC
Dual Therapy - (omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days) (Studies M93-067, M93-100)						
Susceptible[b]	108	72	1		26	9
Intermediate[b]	1				1	
Resistant[b]	4				4	
Triple Therapy - (omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days - Studies 126, 127, M96-446, followed by omeprazole 20 mg q.d. for another 18 days - Studies 126, 127)						
Susceptible[b]	171	153	7		3	8
Intermediate[b]						
Resistant[b]	14	4	1		6	3

[a] Includes only patients with pretreatment clarithromycin susceptibility test results.

[b] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy or omeprazole/clarithromycin dual therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin 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 pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. 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 susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs[1]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 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:

Clarithromycin MIC (µg/mL)[a]	Interpretation	
≤ 0.25	Susceptible	(S)
0.5 - 1.0	Intermediate	(I)
≥ 2.0	Resistant	(R)
Amoxicillin MIC (µg/mL)[a,b]	**Interpretation**	
≤ 0.25	Susceptible	(S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

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:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015 - 0.12 (µg/mL)
H. pylori ATCC 43504	Amoxicillin	0.015 - 0.12 (µg/mL)

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

INDICATIONS AND USAGE

Duodenal Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori*.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.

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 who fail therapy, PRILOSEC with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

Gastric Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

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

Erosive Esophagitis

PRILOSEC 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.)

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g. heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions

PRILOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

Omeprazole

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

Clarithromycin

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.)

Amoxicillin

Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

WARNINGS

Clarithromycin

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.)

Amoxicillin

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND 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.** (See WARNINGS in prescribing information for amoxicillin.)

Antimicrobials

Pseudomembranous colitis has been reported with nearly all antibacterial agents 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. (See WARNINGS in prescribing information for clarithromycin and amoxicillin.)

PRECAUTIONS

General

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

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Information for Patients

PRILOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interactions

Other

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of PRILOSEC.

Combination Therapy with Clarithromycin

Co-administration of omeprazole and clarithromycin have resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended. (See also CONTRAINDICATIONS, Clarithromycin, above. Please refer to full prescribing information for clarithromycin before prescribing.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

[1] National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa FL, January 11-13, 1998.

Pregnancy

Omeprazole

Pregnancy Category C

Teratology 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 for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 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 embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic 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 potential risk to the fetus.

Clarithromycin

Pregnancy Category C. See WARNINGS (above) and full prescribing 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 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased 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 shown for omeprazole 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 mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

PRILOSEC Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

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

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

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. In many instances, the relationship to PRILOSEC was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema

Prilosec® (omeprazole) Delayed-Release Capsules

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia

Respiratory: Epistaxis, pharyngeal pain

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis

Special Senses: Tinnitus, taste perversion

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Combination Therapy for *H. pylori* Eradication

In clinical trials using either dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with omeprazole, clarithromycin, or amoxicillin.

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)— The most frequent adverse experiences observed in clinical trials using combination therapy with PRILOSEC, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking the antimicrobial drugs alone.

For more information on clarithromycin or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.

Dual Therapy (PRILOSEC/clarithromycin)— Adverse experiences observed in controlled clinical trials using combination therapy with PRILOSEC and clarithromycin (n = 346) which differed from those previously described for omeprazole alone were: Taste perversion (15%), tongue discoloration (2%), rhinitis (2%), pharyngitis (1%) and flu syndrome (1%).

For more information on clarithromycin, refer to the clarithromycin package insert, ADVERSE REACTIONS section.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16-45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Lethal doses of omeprazole after single oral administration are about 1500 mg/kg in mice and greater than 4000 mg/kg in rats, and about 100 mg/kg in mice and greater than 40 mg/kg in rats given single intravenous injections. Animals given these doses showed sedation, ptosis, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of PRILOSEC is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

H. pylori Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)— The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Prilosec® (omeprazole) Delayed-Release Capsules

Dual Therapy (PRILOSEC/clarithromycin)— The recommended adult oral regimen is PRILOSEC 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 14 days of PRILOSEC 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 dosing in elderly and renally impaired patients (PRECAUTIONS: General, PRECAUTIONS: Geriatric Use and PRECAUTIONS: Drug Interactions).

Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS.

Gastric Ulcer

The recommended adult oral dose is 40 mg once a day for 4 -8 weeks. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer, and INDICATIONS AND USAGE, Gastric Ulcer.)

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions 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 4 to 8 weeks. (See INDICATIONS AND USAGE.)

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

Pathological Hypersecretory Conditions

The dosage of PRILOSEC in patients with pathological 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. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years.

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

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

Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

HOW SUPPLIED

No. 3426 — PRILOSEC Delayed-Release Capsules, 10 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 606 on cap and PRILOSEC 10 on the body. They are supplied as follows:

NDC 0186-0606-31 unit of use bottles of 30
NDC 0186-0606-68 bottles of 100
NDC 0186-0606-28 unit dose packages of 100
NDC 0186-0606-82 bottles of 1000.

No. 3440 — PRILOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules, coded 742 on cap and PRILOSEC 20 on body. They are supplied as follows:

NDC 0186-0742-31 unit of use bottles of 30
NDC 0186-0742-28 unit dose package of 100
NDC 0186-0742-82 bottles of 1000.

No. 3428 — PRILOSEC Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 743 on cap and PRILOSEC 40 on the body. They are supplied as follows:

NDC 0186-0743-31 unit of use bottles of 30
NDC 0186-0743-68 bottles of 100
NDC 0186-0743-28 unit dose packages of 100
NDC 0186-0743-82 bottles of 1000.

Storage

Store PRILOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F).

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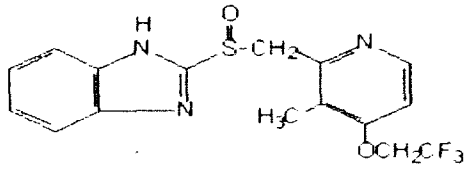
PREVACID®

(prē' 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] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. The structural formula is:



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 (C_{max}) 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 C_{max} 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 C_{max} 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 sulfinyl 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 canaliculus, 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 ^{14}C-lansoprazole, approximately one-third of the administered radiation 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 C_{max} and T_{max} 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 C_{max} 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 H_2-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

		PREVACID				Omeprazole	
	Baseline Value	15 mg		30 mg		20 mg	
Parameter		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
Mean 24-Hour pH	2.1	2.7*	4.0*	3.6*	4.9*	2.5	4.2*
Mean Nighttime pH	1.9	2.4	3.0*	2.6	3.8*	2.2	3.0*
% Time Gastric pH>3	18	33*	59*	51*	72*	30*	61*
% Time Gastric pH>4	12	22*	49*	41*	66*	19	51*

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.
* ($p<0.05$) versus baseline, lansoprazole 15 mg and omeprazole 20 mg
* ($p<0.05$) 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

	PREVACID			
Parameter	30 mg q.d.	15 mg b.i.d.	30 mg b.i.d.	30 mg t.i.d.
% Time Gastric pH>5	43	47	59*	77*
% Time Gastric pH>6	20	23	28	45*
* $p<0.05$ versus PREVACID 30 mg q.d., 15 mg b.i.d. and 30 mg b.i.d.				
† $p<0.05$ versus PREVACID 30 mg q.d.				

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 (T_3), thyroxine (T_4), 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[a]

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative – eradicated	*H. pylori* positive – not eradicated			
			Post-treatment susceptibility results			
			S[b]	I[b]	R[b]	No MIC
Triple Therapy 14-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399, M93-131, M95-392)						
Susceptible[b]	112	105				7
Intermediate[b]	3	3				
Resistant[b]	17	6			7	4
Triple Therapy 10-Day (lansoprazole 30 mg b.i.d./amoxicillin 1 gm b.i.d./clarithromycin 500 mg b.i.d.) (M95-399)						
Susceptible[b]	42	40	1		1	
Intermediate[b]						
Resistant[b]	4	1			3	

[a] Includes only patients with pretreatment clarithromycin susceptibility test results.
[b] Susceptible (S): MIC ≤ 0.25 μg/mL; Intermediate (I): MIC 0.5 – 1.0 μg/mL; Resistant (R): MIC ≥ 2 μg/mL

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.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 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:

Clarithromycin MIC (µg/mL)[a]	Interpretation
≤ 0.25	Susceptible (S)
0.5 – 1.0	Intermediate (I)
≥ 2.0	Resistant (R)
Amoxicillin MIC MIC (µg/mL)[b]	Interpretation
≤ 0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

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:

Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015 – 0.12 mcg/mL
H. pylori ATCC 43504	Amoxicillin	0.015 – 0.12 mcg/mL

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

Reference

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

CLINICAL STUDIES

Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 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

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=68)	(N=74)	(N=70)	(N=72)
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

* (p≤0.001) versus placebo

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

	PREVACID		Ranitidine	Placebo
	15 mg q.d.	30 mg q.d.	300 mg h.s.	
Week	(N=80)	(N=77)	(N=82)	(N=41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3%***	80.3%*	70.5%*	47.5%

* (p≤0.05) versus placebo
** (p≤0.05) versus placebo and ranitidine

***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)

Study	Duration	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis#
M93-131	14 Days	92† [80.0 – 97.7] (N=48)	86† [73.3 – 93.5] (N=55)
M95-392	14 Days	86‡ [75.7 – 93.6] (N=66)	83‡ [72.0 – 90.8] (N=70)
M95-399+	14 Days	85 [77.0 – 91.0] (N=113)	92 [73.9 – 88.1] (N=126)
	10 Days	84 [76.0 – 89.8] (N=123)	81 [73.9 – 87.6] (N=135)

* Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest® (Delta West Ltd., Bentley, Australia), histology and/or culture. Patients were included in the analyses if they completed the study. Additionally, if 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.

Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

† (p<0.05) versus PREVACID/amoxicillin and PREVACID/clarithromycin dual therapy.

‡ (p<0.05) versus amoxicillin/clarithromycin dual therapy.

+ The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day is [-16.5, 8.1] in the evaluable analysis and [-9.7, 9.1] in the intent to treat analysis.

H. pylori Eradication Rates – 14-Day Dual Therapy
(PREVACID/amoxicillin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Dual Therapy Evaluable Analysis*	Dual Therapy Intent-to-Treat Analysis#
M93-131	77† [62.5 – 87.2] (N=51)	70† [56.8 – 81.2] (N=60)
M93-125	66‡ [51.9 – 77.5] (N=58)	61‡ [48.5 – 72.9] (N=67)

* Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and or culture. Patients were included in the analyses if they completed the study. Additionally, if 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.

Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

† (p<0.05) versus PREVACID alone.

‡ (p<0.05) versus PREVACID alone or amoxicillin 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

			Percent in Endoscopic Remission		
Trial	Drug	No. of Pts.	0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID 15 mg q.d.	86	90%*	87%*	84%*
	Placebo	83	49%	41%	39%
#2	PREVACID 30 mg q.d.	18	94%*	94%*	85%*
	PREVACID 15 mg q.d.	15	87%*	79%*	70%*
	Placebo	15	33%	0%	0%

% = Life Table Estimate

* (p<0.001) versus 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

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=65)	(N=63)	(N=61)	(N=64)
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

*p≤0.05 versus 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.

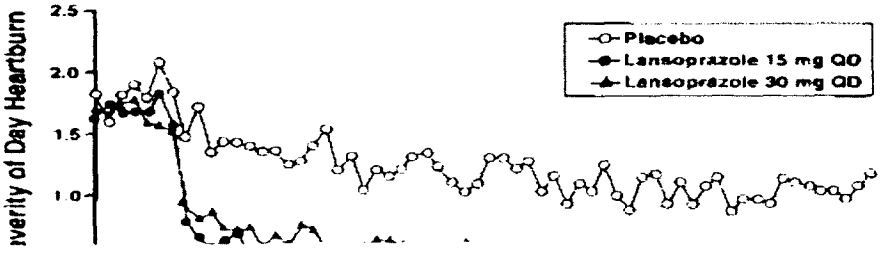
Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD
In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration 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.

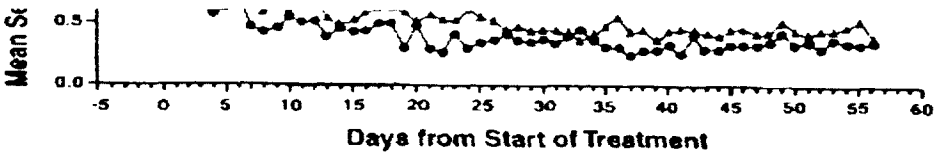
The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

Frequency of Heartburn			
Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
% of Days without Heartburn	Median		
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

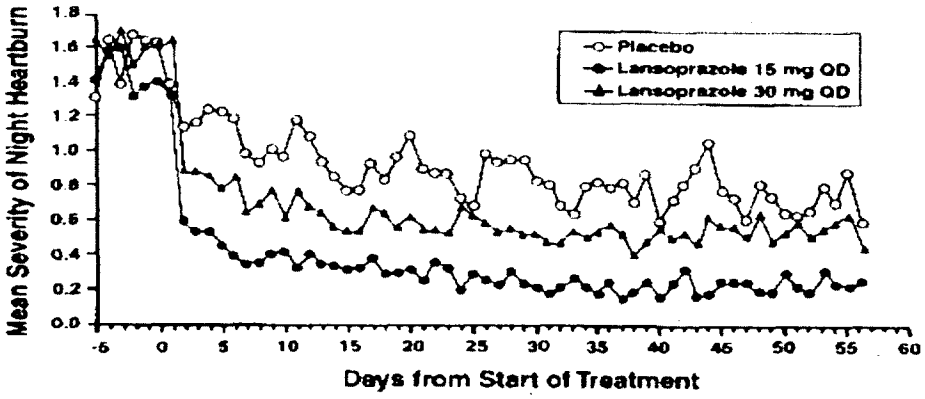
*p<0.01 versus placebo

Mean Severity of Day Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)





Mean Severity of Night Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)



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

	PREVACID			Placebo
	15 mg q.d.	30 mg q.d.	60 mg q.d.	
Week	(N=69)	(N=65)	(N=72)	(N=63)
4	67.6%*	81.3%**	80.6%**	32.8%
6	87.7%*	95.4%*	94.3%*	52.5%
8	90.9%*	95.4%*	94.4%*	52.5%

* $p \leq 0.001$; versus placebo
** $p \leq 0.05$; versus 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

Week	PREVACID 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

* $p \leq 0.001$ versus ranitidine

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 H_2-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 H_2-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H_2-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H_2-receptor antagonist.

Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H_2-Receptor Antagonist Therapy

Week	PREVACID 30 mg q.d. (N=100)	Ranitidine 150 mg b.i.d. (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

* $p \leq 0.001$ 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

			Percent in Endoscopic Remission		
Trial	Drug	No. of Pts	0–3 mo.	0–6 mo.	0–12 mo.
#1	PREVACID 15 mg q.d.	59	83%*	81%*	79%*
	PREVACID 30 mg q.d.	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
#2	PREVACID 15 mg q.d.	50	74%*	72%*	67%*
	PREVACID 30 mg q.d.	49	75%*	72%*	55%*
	Placebo	47	16%	13%	13%

% = Life Table Estimate
* $p \leq 0.001$ 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_{450} 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_{450} 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_{450} 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 (eg, 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/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). 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
See **WARNINGS** (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

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:

Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-term, Placebo-Controlled Studies

Body System/ Adverse Event	PREVACID (N=1457) %	Placebo (N=467) %
Body as a Whole		
Abdominal Pain	1.8	1.3
Digestive System		
Diarrhea	3.6	2.6
Nausea	1.4	1.3

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, cardiospasm, 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/arthralgia, 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, hiccup, 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).

R_x only

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TAP Pharmaceuticals Inc.
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