CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Bacho

Food and Drug Administration
Rockville MD 20857

John M. Provenza, M.D.
Gastrointestinal Specialists, AMC
3217 Mabel Street
Shreveport, Pennsylvania 71103

SEP 19 2000

Dear Dr Provenza:

Between June 27 and July 27, 2000, Mr. Mark W. Rivero, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 192) of the investigational drug Nexium (esomeprazole magnesium), 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 pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations. We are aware that Mr. Rivero discussed with you his inspectional observations at the close of the inspection. The discussion included, but was not limited to, your failure to perform the study according to the relevant protocol in that randomization and stratification procedures were not followed as required by the protocol for subjects #010, #013, #014, and #008. We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the finding discussed above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Rivero during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Bacho

Food and Drug Administration
Rockville MD 20857

SEP 13 2000

Isaac Bassan, M.D.
Pharma Research Group, Inc.
4302 Alton Road, Suite 850
Miami, Florida 33140

Dear Dr Bassan:

Between July 13 and 18, 2000, Ms. Luz I. Collado, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol # 191) of the investigational drug Nexium (esomeprazole magnesium), 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, the documents submitted with that report and your July 27, 2000, written response to the items listed on the Form FDA 483, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations. We are aware that Ms. Collado discussed with you and your staff her inspectional observations at the close of the inspection. The discussion included: a) your failure to handle frozen tissue biopsy samples as required by the protocol for seven subjects (#002, #003, #004, #005, #006, #007 and #008); and b) your failure to maintain source documentation for the baseline CLO test for subjects #003 and #005. We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Collado during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

AstraZeneca

Kathryn Kross
Director

March 7, 2000

Mr. Jeff Fritsch, Regulatory Project Manager
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Mr. Fritsch:

NDA 21-154 Nexium™ (esomeprazole magnesium)
Delayed-Release Capsules (also known as H 199/18)
Response to Request for Information

Reference is made to NDA 21-154 for Nexium™ Delayed-Release Capsules submitted February 28, 2000. Additional reference is made to your telephone conversation on March 3, 2000 with Dr. Gary Horowitz regarding provision of a desk copy of the CMC information from NDA 21-153.

In response to this request, a desk copy consisting of six volumes of the Chemistry, Manufacturing, and Controls Information (volumes 1.5 through 1.10) from NDA 21-153 is attached.

Please direct any questions or requests for additional information me at (610)-695-1873, or in my absence, to Donna Kipphorn, Regulatory Project Manager, at (610) 578-8416.

Sincerely yours,

Kathryn Kross
Director, Regulatory Affairs

FedEx tracking number: [redacted]
Attachment: One desk copy, 6 binders

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

AstraZeneca

Gary P. Horowitz, Ph.D.
Executive Director

10 March 2000

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
HFD-590, Room S445
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-154
NEXIUM™ (esomeprazole magnesium) Delayed-Release Capsules
General Correspondence

Dear Dr. Goldberger:

Please refer to NDA 21-154 for Nexium™ that was submitted February 28, 2000.

I wish to inform you that, effective 15 March 2000, the primary AstraZeneca LP contact for all matters concerning NDA 21-154 is being transferred to Ms. Kathryn D. Kross. She can be reached at the following address and telephone number:

Kathryn D. Kross
Director, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19807-5677
Tel: 610-695-1873
FAX: 610-695-4479

In Ms. Kross' absence, please contact Donna Kipphorn, Regulatory Project Manager, at 610-578-8416.

Sincerely,

Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs

Federal Express No.: _____
Desk Copy: Mr. Jeff Fritsch

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
AstraZeneca LP	10 March 2000
TELEPHONE NO. *(Include Area Code)* 610-695-1873	FACSIMILE (FAX) Number *(Include Area Code)* 610-695-4479
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 725 Chesterbrook Blvd. Wayne, PA 19087-5677	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-154

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
esomeprazole magnesium	Nexium™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate	H 199/18

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Delayed-Release Capsules	20 mg, 40 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

Eradication of Helicobacter Pylori

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION : GeneralCorrespondence

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA 19-810; NDA 21-153

AstraZeneca

Kathryn Kross
Director

March 29, 2000

Mr. Jeff Fritsch, Regulatory Project Manager
Division of Special Pathogens and Immunologic
Drug Products HFD-590 Mail Stop S-416
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Mr. Fritsch:

NDA 21-154 Nexium™ (esomeprazole magnesium)
Delayed-Release Capsules (also known as H 199/18)
Response to Request for Package Insert and Annotated Package Insert

Reference is made to NDA 21-154 for Nexium™ Delayed-Release Capsules submitted February 28, 2000. Additional reference is made to your telephone message to Dr. Gary Horowitz on March 27, 2000 and follow-up conversation with Ms. Donna Kipphorn regarding provision of a desk copy of the electronic version of the package insert (PI) (Item 2) and the annotated package insert.

In response to this request, a Review Aid in Microsoft® Word 97 (desk copy consisting of one volume in a white binder containing a diskette) of the PI (Filename: NDA 21-154 Nexium™ Package Insert.DOC) and the annotated PI (Filename: NDA 21-154 Nexium™ Annotated Package Insert.DOC, and this letter (Filename: JF030700.DOC) is attached.

Please direct any questions or requests for additional information me at (610)-695-1873, or in my absence, to Donna Kipphorn, Regulatory Project Manager, at (610) 578-8416.

Sincerely yours,

Kathryn Kross
Director, Regulatory Affairs

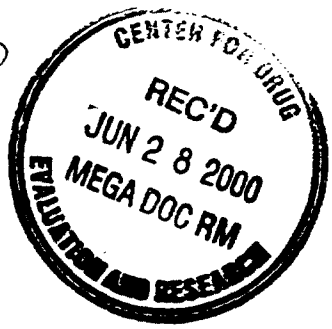
FedEx tracking number: [redacted]
Enclosures: One desk copy, 1 binder

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

AstraZeneca
Kathryn Kross
Director - Regulatory Affairs

NAI
/S/
7/24/00



June 21, 2000

Renata Albrecht, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590, Room S-304
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

AMENDMENT
SU

NDA 21-154 Nexium™ (esomeprazole magnesium) Delayed-Release Capsules
Four Month Safety Update

Dear Dr. Albrecht:

Reference is made to NDA 21-154 for concomitant use of Nexium™ Delayed-Release Capsules (esomeprazole magnesium), clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* (*H. pylori*) submitted to the FDA on February 28, 2000. Reference is also made to NDA 21-153 submitted on December 3, 1999 to the Division of Gastrointestinal and Coagulation Drug Products (GI) the four-month safety update for that NDA submitted April 3, 2000.

With this letter, AstraZeneca is notifying the Agency that no additional safety data from *H. pylori* eradication studies has been obtained since the NDA submission because all pertinent US and International studies to support NDA 21-154 were completed prior to the NDA. Therefore, a four-month safety update (Item 9) will not be provided.

Additional safety information in other indications has been provided in the 4-month safety update document submitted to NDA 21-153. Copies of that update can be provided upon request.

Please direct any questions or requests for additional information to me at (610) 695-1873 or, in my absence, to Donna Kipphorn, Regulatory Project Manager at (610) 578-8416.

Sincerely yours,

Kathryn D. Kross

Kathryn D. Kross
Director, Regulatory Affairs

Copy to Mr. Jeff Fritsch (HFD-590) S-416
Fed Ex Number:

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel +1 610 695 1000
www.astrazeneca-us.com

HFD-590 /J. Fritsch

MAR 6 2000

NDA 21-154

AstraZeneca
Attention: Gary P. Horowitz, Ph.D.
Executive Director
725 Chesterbrook Boulevard
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, 20mg and 40mg

Therapeutic Classification: Standard (S)

Date of Application: February 28, 2000

Date of Receipt: February 28, 2000

Our Reference Number: NDA 21-154

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 April 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 28, 2000 and the secondary user fee goal date will be February 28, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a

determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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 Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Jeffrey Fritsch, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/ for
3/6/00

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-153
IND ———

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

Dear Ms. Kross:

Reference is made to your correspondence dated April 27, 2000, requesting FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We note that this submission provides a rationale for your clinical development program; a synopsis of a proposed pharmacokinetic study of single and multiple dose in pediatric patients aged 2 through 16 years; and a synopsis of a proposed usage study in pediatric patients aged 2 through 16 years in the treatment of gastrointestinal (GI) symptoms associated with acid-related disorders.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request at this time. We are in the process of assimilating information and obtaining external opinion to make a determination as to whether a health benefit would be gained or not gained by studying children for the treatment of GERD and, if so, what ages in the pediatric population would be appropriate to study. Until the Agency completes this determination, a Written Request will not be issued.

If you have any questions, contact Maria R. Walsh, Regulatory Project Manager, at (301) 443-8017.

Sincerely yours,

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

/s/

Lilia Talarico
1/9/01 12:33:07 PM

APPEARS THIS WAY
ON ORIGINAL

FDA REVISED DRAFT LABELING 2/13/01

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 39

Draft

Labeling

FDA REVISED DRAFT LABELING 2/1/01

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 79

Draft

Labeling

FDA APPROVABLE LABELING 10/3/00

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 49

Draft

Labeling

REVISIONS TO PACKAGE INSERT
Submitted 2/14/01

APPEARS THIS WAY
ON ORIGINAL

AstraZeneca

Fax

To	Maria Walsh	**Fax number**	301 443 9285
Company	Food and Drug Administration		
From	Kathy Kross	**Fax number**	619 695 4479
Date	14 February, 2001; 09:25	**Total pages**	1(3)
Subject	NDA 21-153 – Nexium Label		

Dear Maria:

Attached are the editorial revisions for the Nexium label.

Thank you,

Kathy

APPEARS THIS WAY
ON ORIGINAL

AstraZeneca
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000

Microorganism	Antimicrobial Agent	MIC (µg/mL) [a]
H. pylori ATCC 43504	Clarithromycin	0.016 – 0.12 (µg/mL)
H. pylori ATCC 43504	Amoxicillin	0.016 – 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.

Clinical Studies

Healing of Erosive Esophagitis

The healing rates of NEXIUM 40 mg, NEXIUM 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at weeks 4 and 8 were evaluated and are shown in the table below:

Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level *
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	$p < 0.001$
	656	NEXIUM 20 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs omeprazole 20 mg
N.S. = not significant ($p > 0.05$).

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in the table below:

Sustained Resolution[‡] of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent[#] with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level *
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	p <0.001
	620	NEXIUM 20 mg	62.9%	70.1%	N.S.
	626	Omeprazole 20 mg	56.5%	66.5%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	p <0.001
	1188	Omeprazole 20 mg	62.5%	70.8%	

[‡]Defined as 7 consecutive days with no heartburn reported in daily patient diary.
[#]Defined as the cumulative proportion of patients who have reached the start of sustained resolution
*log-rank test vs omeprazole 20 mg
N.S. = not significant (p > 0.05).

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for NEXIUM 40 mg, 7-8 days for NEXIUM 20 mg and 7-9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of NEXIUM with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate NEXIUM 40 mg (n=174), 20 mg (n=180), 10 mg (n= 168) or placebo (n=171) once daily over six months of treatment.

No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

The percentage of patients that maintained healing of erosive esophagitis at the various time points are shown in the figures below:

REVISED PROPOSED PACKAGE INSERT
Submitted 2/12/01 (Afternoon)

APPEARS THIS WAY
ON ORIGINAL

AstraZeneca

Fax

To	Maria Walsh	**Fax number**	301 443-9285
Company	FDA		
From	Kathy Kross	**Fax number**	301 816-8525
Date	12 February, 2001; 15:07	**Total pages**	1(14)
Subject	Revised Nexium Label- Clinical Pharmacology and clinical studies		

Dear Maria:

Per my telephone message, attached is the revised label incorporating revisions agreed upon at the meeting today. Also included are the proposed alternate text for the PK section of the label and a revised definition for heartburn resolution for review by the Division.

I will follow-up with you tomorrow.

Best Regards,
Kathy

APPEARS THIS WAY
ON ORIGINAL

AstraZeneca
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000

WITHHOLD 13

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 2/12/01 (Morning)

WITHHOLD 14

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 2/8/01

APPEARS THIS WAY
ON ORIGINAL

REVISED PROPOSED PACKAGE INSERT
Submitted 2/5/01

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 27

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 12/19/00

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 40

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 8/2/00

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 28

Draft

Labeling

WITHHOLD 29

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 4/3/00

WITHHOLD 28

Draft

Labeling

REVISED PROPOSED PACKAGE INSERT
Submitted 3/17/00

WITHHOLD 23

Draft

Labeling

ORIGINAL PROPOSED PACKAGE INSERT
Submitted 12/3/99

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 17

Draft

Labeling

PROPOSED CONTAINER LABELS
Submitted 12/3/00

APPEARS THIS WAY
ON ORIGINAL

UNIT DOSE PACKAGE OF 100 LABEL - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

UNIT DOSE PACKAGE OF 100
CARTON OVERLAP LABEL - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

UNIT DOSE PACKAGE OF 100
BLISTER CELL - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 30 - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 90 - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 100 - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 1000 - 20 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

UNIT DOSE PACKAGE OF 100 LABEL - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

UNIT DOSE PACKAGE OF 100
CARTON OVERLAP LABEL - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

UNIT DOSE PACKAGE OF 100
BLISTER CELL - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 30 - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 100 - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

BOTTLES OF 1000 - 40 MG

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1

Draft

Label

4.0 FOREIGN MARKETING HISTORY

4.1. H 199/18 Foreign Marketing Status

Currently, H 199/18 is not approved or marketed in any country.

4.2. Omeprazole Marketing Status

From 1988 through 31 January 1999, omeprazole has been approved in 106 countries worldwide.

OCT 24 2000

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

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
October 13, 2000	November 27, 2000	00-0253-2

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 reviewed the firms labeling submission in response to the Division.

OPDRA RECOMMENDATION: OPDRA has further recommendations for labeling revisions to minimize potential errors with the use of this product.

/S/ 10/23/2000
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/ 10/24/00
Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL