

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-153/ 21-154

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21154/000	Priority: 2S	Org Code: 590
Stamp: 28-FEB-2000 Regulatory Due: 28-DEC-2000	Action Goal:	District Goal: 29-OCT-2000
Applicant: ASTRAZENECA	Brand Name: NEXIUM(ESOMEPRAZOLE	
1800 CONCORD PIKE	MAGNESIUM)20/40MG CA	
WILMINGTON, DE 198038355	Established Name:	
	Generic Name: ESOMEPRAZOLE MAGNESIUM	
	Dosage Form: DRC (DELAYED RELEASE CAPSULE)	
	Strength: 20 AND 40 MG	
FDA Contacts: J. FRITSCH (HFD-590)	301-827-2371	, Project Manager
G. HOLBERT (HFD-590)	301-827-2399	, Review Chemist
N. SCHMUFF (HFD-590)	301-827-2425	, Team Leader

Overall Recommendation: .

ACCEPTABLE on 18-SEP-2000 by J. D AMBROGIO (HFD-324)301-827-0062

Establishment: [DMF No:
]	AADA No:

Profile: CTL	OAI Status: NONE	Responsibilities: FINISHED DOSAGE STABILITY
Last Milestone: OC RECOMMENDATION		TESTER
Milestone Date: 06-MAR-2000		
Decision: ACCEPTABLE		
Reason: BASED ON PROFILE		

Establishment: 9615999	DMF No:
ASTRA PRODUCTION TABLETS AB	AADA No:
GARTUNAVAGAN	
SODERTALJE, , SW SK102NA	

Profile: CTR	OAI Status: NONE	Responsibilities: FINISHED DOSAGE
Last Milestone: OC RECOMMENDATION		MANUFACTURER
Milestone Date: 18-SEP-2000		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment: 9615803	DMF No:
ASTRA ZENECA	AADA No:
224 AVENUE DE LA DORDOGNE	
DUNQUERQUE, , FR	

Profile: CSN	OAI Status: NONE	Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION		MANUFACTURER
Milestone Date: 30-AUG-2000		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9612468** DMF No:
ASTRAZENECA RES AND DEV MOLN AADA No:
S-431 83
MOLNDAL, , SW

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE STABILITY**
Last Milestone: **OC RECOMMENDATION** **TESTER**
Milestone Date: **30-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [] DMF No:
AADA No:

Profile: **CTR** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [] DMF No:
AADA No:

Profile: **CTR** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [] DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE STABILITY**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

TESTER

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **06-MAR-2000**

Decision: **ACCEPTABLE**

Reason: **BASED ON PROFILE**

**APPEARS THIS WAY
ON ORIGINAL**

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research**

Proprietary Name Review

DATE OF REVIEW: October 13, 2000

NDA: 21-153

NAME OF DRUG: Nexium (Esomeprazole Magnesium Delayed-release Capsules)
20 mg and 40 mg

NDA HOLDER: AstraZeneca

I. INTRODUCTION

This consult is in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), to evaluate the firms labeling submission in response to requested labeling revisions based on recommendations in our last consult to the Division (See OPDRA Consult 00-0253).

PRODUCT INFORMATION

The proposed generic name for Nexium is esomeprazole magnesium. This drug product is the s-enantiomer of omeprazole, which is marketed as Prilosec Delayed-Release Capsules. The proposed indications are treatment of gastroesophageal reflux disease (GERD) and *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence of healing of erosive esophagitis. Nexium will be available as a delayed-release capsule in unit of use bottles of 30, unit dose packages of 100, bottles of 90, 100 and 1000. Each capsule contains esomeprazole magnesium equivalent to 20 mg or 40 mg of esomeprazole. The recommended dosage and frequency for each indication is as follows:

INDICATION	DOSE	FREQUENCY
Gastroesophageal Reflux Disease (GERD) ⇒Healing of Erosive Esophagitis ⇒Maintenance of Healing of Erosive Esophagitis ⇒Symptomatic Gastroesophageal Reflux Disease	— — 20 mg	Once Daily for 4 to 8 weeks Once Daily Once Daily for 4 weeks
<i>H. pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence <i>Triple Therapy:</i> Nexium Amoxicillin Clarithromycin	40 mg 1000 mg 500 mg	Once Daily for 10 days Twice Daily for 10 days Twice Daily for 10 days

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

A. GENERAL COMMENTS

1. The current expression of the established name and strength is misleading and incorrect since each capsule contains 20 mg or 40 mg of esomeprazole, not 20 mg or 40 mg of esomeprazole magnesium. The strength must be qualified to reflect it is based on the active moiety. This can be accomplished by expressing the established name and strength in one of the following three manners:



OPDRA prefers the first example as an option because this nomenclature is consistent with USP recommendations on “labeling of salts of drugs”.

2. The firm states the revised logo displays the product strength with greater prominence therefore, reducing the risk of confusion with the product strength. We acknowledge this comment, however the font size of the quantity is still too prominent and request the labels and labeling be revised to further decrease the prominence of the number.
3. A space should be placed between the “number” and “mg” in the strength (i.e., 20 mg, 40 mg rather than 20mg, 40mg).

B. UNIT DOSE BLISTER (20 mg and 40 mg)

See GENERAL COMMENTS 1 and 3 above.

C. UNIT DOSE CARTON (100s – 20 mg and 40 mg)

1. See GENERAL COMMENTS.
2. We acknowledge the sponsor's comments regarding the distribution of the unit dose blister packaging. However, unit dose packaging is often dispensed for patients on pass or discharge from the hospital. In this light, it is important that the pharmacist knows that the unit dose blister is not child resistant so that adequate precautions may be taken. Therefore, OPDRA recommends the inclusion of the following statement:

This unit-dose package is not child resistant.

2. OPDRA encouraged the inclusion of an "Each capsule contains..." statement, however the sponsor states that due to space constraints on the container labels they are unable to include this statement. OPDRA believes this is an important statement because the strength must be qualified so it is not misleading. The firm should delete the following statement in order to provide the necessary space for the "Each capsule contains..." statement:

All trademarks are the property...

D. UNIT OF USE BOTTLES (30s – 20 mg and 40 mg)

1. See GENERAL COMMENTS and comments under UNIT DOSE CARTON.
2. We acknowledge the sponsor's comments regarding the — caps that will be utilized in conjunction with these container sizes and finds them acceptable.

E. CONTAINER LABELS (30s, 90s, 100s and 1000s)

See GENERAL COMMENTS and comments under UNIT DOSE CARTON.

**APPEARS THIS WAY
ON ORIGINAL**

IV. RECOMMENDATIONS

OPDRA recommends the above labeling revisions, which might lead, to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-3244.

/S/

10-18-00

Carol Holquist, RPh. ✓
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

10/23/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research**

Proprietary Name Review

DATE OF REVIEW: September 25, 2000

NDA: 21-153

NAME OF DRUG: Nexium (Esomeprazole Magnesium Delayed-release Capsules)
20 mg and 40 mg

NDA HOLDER: AstraZeneca

I. INTRODUCTION

This consult is in response to a September 21, 2000, request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), to re-evaluate the proposed trade name Nexium prior to approval and to review the container labels, carton and insert labeling for interventions that might minimize medication errors.

OPDRA was originally consulted on October 25, 1999 for assessment of the tradename Nexium, regarding potential name confusion with other proprietary/generic drug names. OPDRA had no objections to the use of the proprietary name at that time, however, we did not recommend the use of the established name, esomeprazole magnesium, due to potential confusion with omeprazole (See OPDRA Consult 99-073).

PRODUCT INFORMATION

The proposed generic name for Nexium is esomeprazole magnesium. This drug product is the s-enantiomer of omeprazole, which is marketed as Prilosec Delayed-Release Capsules. The proposed indications are treatment of gastroesophageal reflux disease (GERD) and *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence of healing of erosive esophagitis. Nexium will be available as a delayed-release capsule in unit of use bottles of 30, unit dose packages of 100, bottles of 90, 100 and 1000. Each capsule contains esomeprazole magnesium equivalent to 20 mg or 40 mg of esomeprazole. The recommended dosage and frequency for each indication is as follows:

INDICATION	DOSE	FREQUENCY
Gastroesophageal Reflux Disease (GERD) ⇒Healing of Erosive Esophagitis ⇒Maintenance of Healing of Erosive Esophagitis ⇒Symptomatic Gastroesophageal Reflux Disease	— — 20 mg	Once Daily for 4 to 8 weeks Once daily Once Daily for 4 weeks
<i>H. pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence <i>Triple Therapy:</i> Nexium Amoxicillin Clarithromycin	40 mg 1000 mg 500 mg	Once Daily for 10 days Twice Daily for 10 days Twice Daily for 10 days

II. RISK ASSESSMENT

In our last review, it was noted that the established name, esomeprazole magnesium, was very similar to omeprazole and we expressed our concerns regarding the potential for serious patient outcomes if the two drugs were confused. Esomeprazole is the s-enantiomer of omeprazole, however, it is not indicated

OPDRA recommended the FDA representative to the USAN council (Dr. Dan Boring) be advised of our concerns.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In addition to the above safety concern, we recommend the following labeling revisions, which might minimize potential user error.

A. GENERAL COMMENTS

- As noted in the USP (General Notices, pg. 12) the strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling. We note the product strength currently reflects the amount of the active moiety (Esomeprazole) contained in each tablet. However, the established name reflects the salt (Esomeprazole Magnesium). The way the strength is currently presented could lead you to believe each capsule contains 20 mg and/or 40 mg of Esomeprazole Magnesium rather than 20 mg and/or 40 mg Esomeprazole. We recommend the established name and expression of strength be revised on all labels and labeling to read:

NEXIUM
(Esomeprazole Delayed-release Capsules)
20 mg

If space permits, an "Each capsule contains..." statement (as seen below under package insert) could be included.

2. Several post-marketing medication errors result from similar packaging configurations. When comparing the packaging of the 20 mg and 40 mg capsules, they appear identical. We encourage the sponsor to differentiate the product strengths with the use of boxing, contrasting colors or some other means.
3. The "net quantity" should be relocated so it does not appear in conjunction with the established name so it is not confused for the product strength.

B. UNIT DOSE BLISTER (20 mg and 40 mg)

1. See GENERAL COMMENTS above.
2. Each blister package contains only one capsule and therefore, the established name should be revised to read "Delayed-Release Capsule" rather than "Capsules".

C. UNIT DOSE CARTON (100s – 20 mg and 40 mg)

1. See GENERAL COMMENTS.
2. A statement should be included as to whether or not the unit-dose package is child-resistant. If it is not child-resistant we encourage the inclusion of a statement that if dispensed outpatient, it should be with a child-resistant container. For example:

[]

[Note: The second sentence is optional.]

3. We encourage the inclusion of an "Each capsule contains..." statement.

D. UNIT OF USE BOTTLES (30s – 20 mg and 40 mg)

1. See GENERAL COMMENTS and comments under UNIT DOSE CARTON.
2. We note this package size is a unit of use bottle. The container-closure should be child resistant to be in compliance with the Poison Prevention Act.

E. CONTAINER LABELS AND CARTON LABELING (30s, 90s, 100s and 1000s)

See GENERAL COMMENTS and comments under UNIT DOSE CARTON.

F. PACKAGE INSERT

DESCRIPTION section – Revise the following to read:

[]

IV. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name, Nexium and also recommends the above labeling revisions, which might lead, to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-3244.

/S/ 9-28-00
Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/
Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

NOV 29 1999

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: November 17, 1999
IND#: _____
NAME OF DRUG: Nexium
(esomeprazole magnesium)
IND HOLDER: AstraZeneca LP

I. INTRODUCTION

This consult is in response to a request sent on October 25, 1999, from the Division of Gastro-Intestinal and Coagulation Drug Products, to review a proposed proprietary drug name, Nexium, regarding potential name confusion with other proprietary/generic drug names. The container labels and carton labeling were not available for review of possible interventions in minimizing medication errors.

PRODUCT INFORMATION

The proposed generic name for Nexium is esomeprazole magnesium. This drug product is the s-enantiomer of omeprazole which is marketed as Prilosec Delayed-Release Capsules. The proposed indications are acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (GERD). AstraZeneca intends to submit a subsequent indication for the eradication of Helicobacter pylori in combination with antibiotics in the 1st quarter of 2000. According to the Division's project manager, this proposed product is available as _____ 20 mg, and 40 mg capsules. For the treatment of GERD, 20 mg daily (QD) for 4 weeks is recommended. For acute and maintenance erosive esophagitis, the recommended doses are _____ QD for 4 to 8 weeks and _____ QD _____ respectively.

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, Nexium, with other drug names, the medication error staff of OPDRA searched American Drug Index (42nd Edition), Drug Facts and Comparisons (1998 Edition), PDR (53rd Edition, 1999), Drug Product Reference File (DPRF), and EES (Established Evaluation System) for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted studies of written and verbal analysis of the proposed proprietary

name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. Study conducted within OPDRA

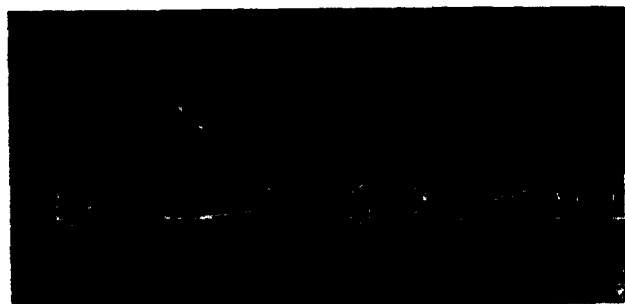
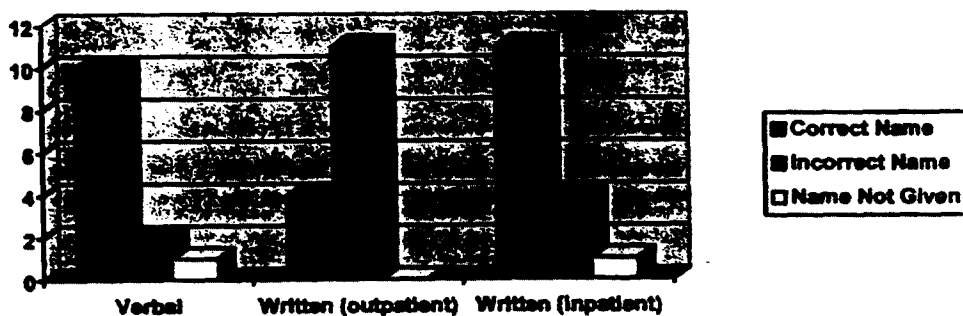
1) Methodology

This study involved 54 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Nexium with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions vial e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals. The medication error staff then reviewed the handwriting samples of the names.

2) Results

We received forty-four interpretations of the proposed proprietary name, Nexium, from the participants. Thirteen interpretations of verbal orders, fifteen interpretations of outpatient written orders, and sixteen interpretations of inpatient written orders were received. Twenty-five participants interpreted Nexium correctly and seventeen incorrectly interpreted the name. Two participants did not provide a name. The results are as follows:

Nexium



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Incorrect names include: Nexiuim, Nexiamin, Nexsium, Nexiam(3), Nexiwan(2), Neviramine, Nexuim, Rexiun, Mevacor, Nexin, Nexiarm, Rexium, & Nexiun

B. Discussion

The results of the verbal and written analyses demonstrate that the majority of the participants correctly interpreted the proprietary name, Nexium. However, there were some concerns by participants that Nexium could be confused for existing proprietary names. One participant actually interpreted Nexium as Mevacor. Another participant, who correctly interpreted Nexium, suggested that when the name is scripted, it looks similar to Noroxin, Norvir, and Flexeril, and therefore, may cause name confusion. Furthermore, a participant, who also correctly interpreted the name, suggested that Nexium sounds-alike _____ when verbally communicated.

After reviewing these suggested names, we find that there is insufficient evidence to predict that Nexium will be confused with Noroxin, Mevacor, Norvir, Flexeril, and/or _____ due to look-alike or sound-alike names. Furthermore, these names, except Mevacor, were suggested by practitioners who interpreted the proposed proprietary name correctly in the study. In addition, searches in available texts, databases, and the handwriting samples did not produce any significant new information to render the proposed proprietary name objectionable.

C. Focus Group Findings

The proposed established name, esomeprazole magnesium, is very similar to omeprazole. Although esomeprazole magnesium is the s-enantiomer of omeprazole, this proposed drug is not indicated _____

_____ Since these two drug products have similar established names and different indications for certain medical conditions, medication errors may occur, resulting in significant outcomes. For example, a patient with _____ could receive esomeprazole magnesium instead of omeprazole due to name confusion. Since esomeprazole magnesium is not indicated for _____, it may lack efficacy in the treatment of _____ for this patient. Furthermore, since the treatment doses for erosive esophagitis are different for these two drugs, patients who receive esomeprazole magnesium instead of omeprazole, may be underdosed. In addition, identical drug strengths (i.e. _____ 20 mg) and dosing schedule (for GERD) may further contribute to the confusion of these two drugs.

III. RECOMMENDATIONS

- A. OPDRA has no objections to the use of the proprietary name, Nexium.
- B. OPDRA does not recommend the use of the established name, esomeprazole magnesium, due to the potential confusion with omeprazole. The FDA representative to the USAN council (Dan Boring) should be advised of our concern.

- C. This name should be resubmitted to OPDRA within 60 days of NDA approval in order to determine if there are other names approved from this date forth that would render Nexium objectionable. The applicant should be advised of this procedure.
- D. The container label and carton labeling were not available for review of possible interventions in minimizing medication errors.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

/S/

11/29/99

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

11/29/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC: Office Files

HFD-180: Maria Walsh, Consumer Safety Officer, Division of
Gastro-Intestinal and Coagulation Drug Products

HFD-400: Jerry Phillips, Associate Director, OPDRA

HFD-400: Peter Honig, Deputy Director, OPDRA

HFD-2 : Mac Lumpkin, Acting Director, OPDRA

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 20, 2001

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

SUBJECT: Nexium (esomeprazole magnesium H199/18)

TO: NDA 21-153

Nexium (esomeprazole magnesium, H199/18) is the *s*-enantiomer of the proton pump inhibitor (PPI) omeprazole. As the parent compound, esomeprazole suppresses gastric acid secretion through dose-related inhibition of the H⁺/K⁺ - ATPase enzyme system.

Based on the claim that esomeprazole has a metabolic profile that may differ from that of omeprazole, the sponsor has performed the clinical development of this enantiomer for gastroesophageal reflux disease (GERD), including healing of erosive esophagitis (EE), maintenance of healing of EE and treatment of symptomatic GERD in addition to eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence.

On December 3, 1999, the sponsor submitted an NDA (NDA 21-153) for the marketing approval of Nexium for the following indications:

- 1) healing of erosive esophagitis,
- 2) maintenance of healing of EE,
- 3) treatment of symptomatic gastroesophageal reflux disease.

NDA 21-153 was reviewed by Dr. Gallo-Torres with the recommendation that esomeprazole be approvable for the above indications with labeling changes including the recommendation for the dose regimen of 20 mg/qd for the for the indication of healing of EE.

On October 16, 1999, the sponsor responded to the approvable letter with the submission of a document that addressed the difference in the metabolic profile of esomeprazole and omeprazole and the efficacy data from the clinical trials of healing of EE to support the sponsor's recommendation for the 40 mg/qd dose regimen. A revised labeling was submitted.

This review will address only the esomeprazole indication for healing and maintenance of EE and the clinical trials submitted in the NDA to support the sponsor's recommendation

of the dose regimen. Dr. Gallo-Torres's medical review and the Biopharm review can be referenced for information regarding the PK and PD characteristics of esomeprazole.

The clinical development of esomeprazole was initiated in 1997 when the sponsor submitted three study protocols for the acute healing of EE. Study 172 was a double blinded, three arm study that compared esomeprazole 40 and 20 mg qd to omeprazole 20 mg qd for 8 weeks. Study 173 compared esomeprazole 40 mg/qd to omeprazole 20 mg/qd for 8 weeks. At completion of study 172, responders were randomized to a four arm study of maintenance therapy with esomeprazole 10, 20 or 40 mg/qd or placebo for 6 months. Study 174 compared esomeprazole 20 mg/qd to omeprazole 20 mg/qd for 8 weeks followed by open-label maintenance therapy with esomeprazole 40 mg/qd for 12 months.

Because the healing rates for omeprazole 20 mg/qd in studies 173 and 174 were higher than the anticipated rate of 75% (90% and 88% respectively) and not significantly different from esomeprazole 40 mg/qd, a fourth study (study 222) was subsequently designed to demonstrate statistically significant difference in healing rates for esomeprazole 40 mg/qd and omeprazole 20 mg/qd. The study was powered to show a 5% difference in healing rates between the two treatment groups.

All four clinical trials were considered to be pivotal.

The results of the four trials are summarized in the following tables.

Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Group	Week 4 of therapy	Week 8	Significance *
#172	654	Esomeprazole 40 mg	75.9%	94.1%	P<0.001
	656	Esomeprazole 20 mg	70.5%	89.9%	P<0.05%
	650	Omeprazole 20 mg	64.7%	86.9%	
#173	576	Esomeprazole 40 mg	71.5%	92.2%	NS
	572	Omeprazole 20 mg	68.6%	89.9%	
#174	588	Esomeprazole 20 mg	68.7%	90.6%	NS
	588	Omeprazole 20 mg	69.5%	88.3%	
#222	1216	Esomeprazole 40 mg	81.7%	93.7%	P<0.001
	1209	Omeprazole 20 mg	68.7%	84.2%	

* Compared to Omeprazole 20 mg

NS=not significant (p>0.05)

Efficacy for healing of EE was established at both dose regimens of esomeprazole 40 mg/qd and 20 mg/qd compared to omeprazole 20 mg/qd. In two studies, esomeprazole 40 mg/qd resulted in statistically higher healing rates than omeprazole 20 mg/qd, however, esomeprazole 20 mg/qd was not significantly different from omeprazole 20 mg/qd.

Analyses of the secondary endpoints of sustained resolution of heartburn by week 4 showed greater rate of responders for the esomeprazole 40 mg/qd in two studies that

compared these regimens to omeprazole 20 mg/qd. No difference was noted between the esomeprazole 20 mg/qd and the omeprazole 20 mg/qd treatment groups.

Since the difference between the esomeprazole 20 mg/qd and the omeprazole 20 mg/qd observed in study 172 was not reproduced in study 174, the observed differences in healing rates and symptom relief for esomeprazole 40 mg and omeprazole 20 mg may reflect differences in dose rather than metabolic or pharmacologic differences. No clinical comparison of 40 mg of esomeprazole with 40 mg of omeprazole were performed to quantify the effect of metabolic differences of this dose.

In addition to EE, esomeprazole has been evaluated for the treatment of symptomatic GERD in five clinical trials, two placebo-controlled, and three with omeprazole 20 mg/qd as comparator. Esomeprazole at 20 mg/qd and 40 mg/qd was statistically significantly superior to placebo. No significant difference was noted between the 20 and 40 mg/qd doses of esomeprazole and between 40 or 20 mg/qd of esomeprazole and 20 mg/qd of omeprazole.

The efficacy of esomeprazole for maintenance of healing of EE was evaluated in two double-blind clinical trials that enrolled patients from study 172 with healed EE. Three daily dose levels of esomeprazole of 40 mg, 20 mg and 10 mg to placebo for 6 months. All three dose regimens of esomeprazole were significantly superior to placebo (p-value <0.001) for the proportion of patients with healed EE through the 6 months of treatment. No significant difference was noted for the esomeprazole 40 and 20 mg/qd.

No differences in safety among the treatment regimens of esomeprazole 40, 20 mg/qd or omeprazole 20 mg/qd were observed.

In conclusion, the results of the studies have demonstrated that esomeprazole is safe and effective for the healing of EE. The results of the clinical trials support both esomeprazole regimens of 20 and 40 mg/qd for the healing of EE. Both dose regimens are recommended for approval, but there is no information on when to choose one over the other.

Labeling revisions agreed upon by the Agency and by the sponsor were finalized on 2-12-2001.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Lilia Talarico
2/20/01 04:34:17 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



Gary P. Horowitz, Ph.D.
Executive Director

January 28, 2000

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

NDA 21-154; Nexium™ (H 199/18) Delayed-Release Capsules
User Fee I.D. Number: 3865

In accordance with The Prescription Drug User Fee Act of 1992, as amended by the Food and Drug Administration Modernization Act of 1997, two checks (check number _____ in the amount of _____ and check number _____ in the amount of _____, totaling _____ which represents the 2000 User Fee for applications requiring clinical data, are being sent to the Food and Drug Administration, Pittsburgh, PA in support of the above referenced NDA. This NDA will be submitted to the Division of Special Pathogens and Immunologic Drug Products (HFD-590) in February.

We consider the fact of filing this New Drug Application to be a confidential matter and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of AstraZeneca LP.

Please direct any questions or requests for additional information to me at 610-695-1008 or, in my absence, to Donna Kipphorn, Regulatory Project Manager, at 610-695-8416.

Sincerely yours,

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

FedEx Tracking No.: _____

Sent to: Mellon Bank
Three Mellon Bank Center
27th Floor (FDA PO Box 360909)
Pittsburgh, PA 15259-0001

Enclosures

- Copy of Form FDA 3397 (User Fee Cover Sheet)
- 1 AstraZeneca LP User Fee Check (Check No. _____)
- 1 AstraZeneca LP User Fee Check (Check No. _____)
- Desk Copy (letter only) to Jeff Fritsch, Regulatory Project Manager, (HFD-590)

ITEM 13
PATENT INFORMATION

**APPEARS THIS WAY
ON ORIGINAL**

II. Patent Information

The patent information for Nexium™ (esomeprazole magnesium) is provided in this section. Twelve (12) patents have been identified as pertinent to the capsule formulation of Nexium and its indication for the treatment of Helicobacter pylori - associated duodenal ulcer.

Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2).

<u>Patent Number</u>	<u>Date of Patent Expiry</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
4255431	5 April 1999 PTE 5 April 2001	Drug substance, drug product and method of use	Astra AB	AstraZeneca LP
4738974	19 April 2005	Drug substance, drug product and method of use	AB Hässle	AstraZeneca LP
4636499	30 May 2005	Drug substance	AB Hässle	AstraZeneca LP
5900424	4 May 2016	Drug substance and method of use	Astra AB	AstraZeneca LP
4786505	20 April 2007	Drug product and method of use	AB Hässle	AstraZeneca LP
4853230	20 April 2007	Drug product and method of use	AB Hässle	AstraZeneca LP

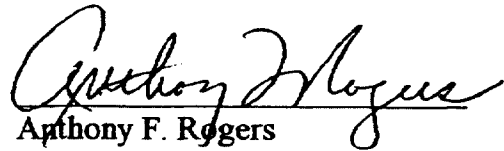
<u>Patent Number</u>	<u>Date of Patent Expiry</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
5714504	3 February 2015	Drug product and method of use	Astra AB	AstraZeneca LP
5877192	27 May 2014	Method of use	Astra AB	AstraZeneca LP
5093342	2 February 2010	Method of use	AB Hässle	AstraZeneca LP
5599794	4 February 2014	Drug product and method of use	Astra AB	AstraZeneca LP
5629305	4 February 2014	Drug product and method of use	Astra AB	AstraZeneca LP
5690960	25 November 2014	Drug product and Method of use	Astra AB	AstraZeneca LP

**APPEARS THIS WAY
ON ORIGINAL**

II. Patent Declaration Statement

DECLARATION

The undersigned declares that U.S. Patent Numbers 4255431, 4738974, 5900424, 4786505, 4853230, 5714504, 5877192, 5093342, 5599794, 5629305 and 5690960 cover the formulation, composition and/or method of use of Nexium™ (esomeprazole magnesium). This product is the subject of this application for which approval is being sought.



Anthony F. Rogers
Vice President, Regulatory Affairs
AstraZeneca LP

**APPEARS THIS WAY
ON ORIGINAL**

I. Patent Information

In accordance with Title CFR § 314.53(2)(iii), revised patent information for Nexium™ (esomeprazole magnesium) is provided in this section. The patent information has been amended to include Patent Number 5690960. Twelve (12) patents have been identified as pertinent to the capsule formulation for Nexium and its indications for the treatment of gastroesophageal reflux disease (GERD), and for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence.

Patent information as per Title 21 CFR § 314.53 (c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53 (c)(2).

<u>Patent Number</u>	<u>Date of Patent Expiry</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
4255431	5 April 1999 PTE 5 April 2001	Drug substance, drug product and method of use	Astra AB	AstraZeneca LP
4738974	19 April 2005	Drug substance, drug product and method of use	AB Hässle	AstraZeneca LP
4636499	30 May 2005	Drug substance	AB Hässle	AstraZeneca LP
5900424	4 May 2016	Drug substance and method of use	Astra AB	AstraZeneca LP
4786505	20 April 2007	Drug product and method of use	AB Hässle	AstraZeneca LP
4853230	20 April 2007	Drug product and method of use	AB Hässle	AstraZeneca LP

**APPEARS THIS WAY
ON ORIGINAL**

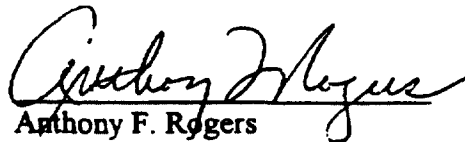
<u>Patent Number</u>	<u>Date of Patent Expiry</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
5714504	3 February 2015	Drug product and method of use	Astra AB	AstraZeneca LP
5877192	27 May 2014	Method of use	Astra AB	AstraZeneca LP
5093342	2 February 2010	Method of use	AB Hässle	AstraZeneca LP
5599794	4 February 2014	Drug product and method of use	Astra AB	AstraZeneca LP
5629305	4 February 2014	Drug product and method of use	Astra AB	AstraZeneca LP
5690960	25 November 2014	Drug product and Method of use	Astra AB	AstraZeneca LP

APPEARS THIS WAY
ON ORIGINAL

II. Patent Declaration Statement

DECLARATION

The undersigned declares that U.S. Patent Numbers 4255431, 4738974, 5900424, 4786505, 4853230, 5714504, 5877192, 5093342, 5599794, 5629305 and 5690960 cover the formulation, composition and/or method of use of Nexium™ (esomeprazole magnesium). This product is the subject of this application for which approval is being sought.




Anthony F. Rogers
Vice President, Regulatory Affairs
AstraZeneca LP

**APPEARS THIS WAY
ON ORIGINAL**

1.0 DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 335a(k)) as amended by the Generic Drug Enforcement Act of 1992 (GDEA), AstraZeneca LP (formerly Astra Pharmaceuticals, L.P. until June 1, 1999 and also known as Astra Merck, Inc. until July 1, 1998) hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] in connection with this application,



Gary P. Horowitz, Ph.D.

Executive Director of Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

1.0 DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, AstraZeneca LP (formerly Astra Pharmaceuticals, L.P. until June 1, 1999 and also known as Astra Merck, Inc. until July 1998) did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.



Gary P. Horowitz, Ph.D.

Executive Director of Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

ITEM 14

PATENT CERTIFICATION

NOT APPLICABLE

This application is not a 505(b)(2) application; therefore, the Patent Certification as described under 21 U.S.C. 335(b)(2) or (j)(2)(A) and 21 CFR 314.50(I) is not required.

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-154

Trade Name: Nexium

Generic Name: esomeprazole ,

Applicant Name: AstraZeneca LP

HFD-590

Approval Date: 12/15/2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/X/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /X/

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a): If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
 Investigation #2 YES /___/ NO /___/
 Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____
 Investigation #__, Study # _____
 Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	!	
IND # _____	!	YES /___/
	!	NO /___/ Explain: _____
	!	_____
	!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title: _____

Date

Signature of Office of Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

**APPEARS THIS WAY
ON ORIGINAL**

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

EXCLUSIVITY SUMMARY for NDA # 21-153
Trade Name: Nexium Delayed-Release Capsules
Generic Name: esomeprazole magnesium

SUPPL # _____

Applicant Name: AstraZeneca LP
Approval Date: 2/20/01

HFD-180

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO /___/

b) Is it an effectiveness supplement? YES /___/ NO / X /

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ___ / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-810 Prilosec (omeprazole) Delayed-Release Capsule

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___/ NO / ___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___/ NO / X /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___/ NO / ___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / X /

If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Indication #1: Healing of Erosive Esophagitis

Investigation # 1, Study # 172

Investigation # 2, Study # 173

Investigation # 3, Study # 174

Investigation # 4, Study # 222

Indication #2: Maintenance of Healing Of Erosive Esophagitis

Investigation # 5 Study # 177

Investigation # 6, Study # 178

Indication #3: Treatment of Symptomatic GERD

Investigation # 7, Study # 225

Investigation # 8, Study # 226

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO / X /
Investigation #2	YES /___/	NO / X /
Investigation #3-8	YES /___/	NO /-X /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO / X /
Investigation #2	YES /___/	NO / X /
Investigation #3-8	YES /___/	NO / X /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # 172

Investigation # 2, Study # 173

Investigation # 3, Study # 174

Investigation # 4, Study # 222

Investigation # 5, Study # 177

Investigation # 6, Study # 178

Investigation # 7, Study # 225

Investigation # 8, Study # 226

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # YES / X / NO / / Explain:
!
!
!
!
!

Investigation #2-8
IND # YES / X / NO / / Explain:
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	:	
YES /___/ Explain _____	:	NO /___/ Explain _____
_____	:	_____
_____	:	_____
Investigation #2	:	
YES /___/ Explain _____	:	NO /___/ Explain _____
_____	:	_____
_____	:	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

Signature of Preparer
Title: _____

Date

Signature of Office of Division Director

Date

CC:
Archival NDA 21-153
HFD-180/Division File
HFD-180/RPM/M.Walsh
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Lilia Talarico
2/20/01 04:32:36 PM

**APPEARS THIS WAY
ON ORIGINAL**

Division of Gastrointestinal & Coagulation Drug Products

JAN 18 2001

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-153

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

Sponsor: AstraZeneca LP

Material Reviewed

Submission Date(s): December 19, 2000

Receipt Date(s): December 20, 2000

Background and Summary Description: The sponsor has submitted revised draft labeling in response to the December 15, 2000 approvable letter.

Review

The submitted draft labeling, dated December 19, 2000, was compared to the draft labeling attached to the December 15, 2000 approvable letter. The following differences were noted.

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WITHHOLD 4

Draft

Labeling

Conclusions

The submitted draft labeling should be reviewed by the biopharmaceutics reviewer. All revisions made by the Agency will be communicated to the sponsor via a marked-up copy of the draft labeling.

 /S/
Maria R. Walsh, M.S.
Regulatory Project Manager

1/18/01

Attachment:

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 13

Draft

Labeling

NDA 21-153

Page 20

cc:

Original NDA 21-153

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-180/L. Talarico

final: M. Walsh 1/18/01

filename: _____

PM REVIEW

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Maria Walsh
1/18/01 12:14:34 PM
CSO

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