CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-153/S015

Trade Name: Nexium Delayed Release Capsules

Generic Name: esomeprazole magnesium

Sponsor: AstraZeneca LP

Approval Date: April 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-153/015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-153/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-153/S-015

Astra Zeneca LP
Wilmington, DE 19803-8355
Attention: George Kummeth, Director Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

Please refer to your supplemental new drug application dated October 23, 2003, received October 24, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium® (esomeprazole magnesium) Delayed-Release Capsules.

This supplemental new drug application provides for changes to the **Adverse Reactions, Postmarketing Reports** section of the Nexium package insert.

We completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (package insert submitted October 23, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-153/S-015." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane

Rockville, MD 20857

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions call, Melissa Hancock Furness, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
4/23/04 12:32:42 PM
for Dr. Robet Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-153/S015

LABELING

NDA 21-153

October 7, 2003

DELETIONS INDICATED BY ~~STRIKETHRU~~, ADDITIONS INDICATED BY DOUBLE UNDERLINING

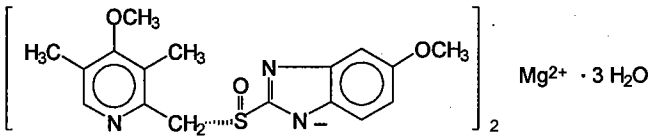
NEXIUM®
(esomeprazole magnesium)
DELAYED-RELEASE CAPSULES

Rx only

Revisions located on page 22

DESCRIPTION

The active ingredient in NEXIUM (esomeprazole magnesium) Delayed-Release Capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:



The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water.

The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

NEXIUM is supplied as Delayed-Release Capsules for oral administration. Each delayed-release capsule contains 20 mg or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a

single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on day 1 to 11.2 μmol*hr/L on day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of NEXIUM over a period of five days. The results are shown in the following table:

Pharmacokinetic Parameters of NEXIUM Following Oral Dosing for 5 days

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
AUC (μmol*h/L)	12.6	4.2
Coefficient of variation	42%	59%
C_{max} (μmol/L)	4.7	2.1
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2

Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor metabolizers. At steady state, the ratio of AUC in Poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion
The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations
Geriatric
The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric
The pharmacokinetics of esomeprazole have not been studied in patients < 18 years of age.

Gender
The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency
The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded (See **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency
The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

Pharmacokinetics: Combination Therapy with Antimicrobials
Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

Pharmacodynamics

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Antisecretory Activity

The effect of esomeprazole on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, NEXIUM 40 mg and 20 mg capsules were administered over 5 days. The results are shown in the following table:

Effect on Intragastric pH on Day 5 (N=36)

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
% Time Gastric pH >4[†] (Hours)	70%* (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%

[†] GASTRIC PH WAS MEASURED OVER A 24-HOUR PERIOD
*P< 0.01 NEXIUM 40 MG VS NEXIUM 20 MG

In a second study, the effect on intragastric pH of NEXIUM 40 mg administered once daily over a five day period was similar to the first study, (% time with pH>4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of NEXIUM on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell 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 3,000 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.

In over 1,000 patients treated with NEXIUM (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NEXIUM on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Microbiology

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori) in vitro* and in clinical infections as described in the **Clinical Studies** and **INDICATIONS AND USAGE** sections.

Helicobacter

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance

Clarithromycin pretreatment resistance rate (MIC ≥ 1 µg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤ 0.25 µg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 µg/mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes

The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in the table below:

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes [a] for Triple Therapy - (Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)

Clarithromycin Pretreatment Results	*H. pylori* negative (Eradicated)	*H. pylori* positive (Not Eradicated) Post-treatment susceptibility results			
		S[b]	I[b]	R[b]	No MIC
Susceptible[b] 182	162	4	0	2	14
Intermediate[b] 1	1	0	0	0	0

Resistant[b]	29	13	1	0	13	2

[a]Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results
[b]Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC =0.5 µg/mL, Resistant (R) MIC ≥ 1.0 µg/mL

Patients not eradicated of *H. pylori* following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes
In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori
The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs. One to three microliters of an inoculum equivalent to a No.2 McFarland standard (1×10^7 - 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 *Campylobacter*. 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	Intermediate	(I)
≥1.0	Resistant	(R)

Amoxicillin MIC (µg/mL)[a,b]	Interpretation	
≤ 0.25	Susceptible	(S)

[a] These are 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	0.016 – 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%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	

4	1187 1188	NEXIUM 40 mg Omeprazole 20 mg	67.6% 62.5%	75.1% 70.8%	p <0.001

‡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.

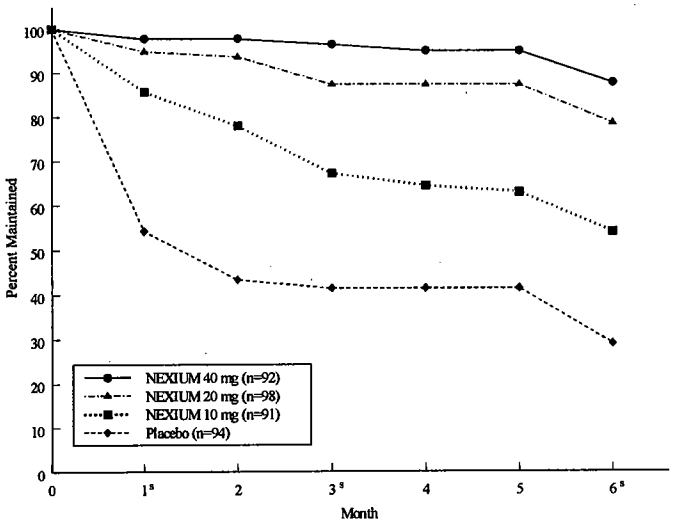
Long-Term Maintenance of Healing of Erosive Esophagitis

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.

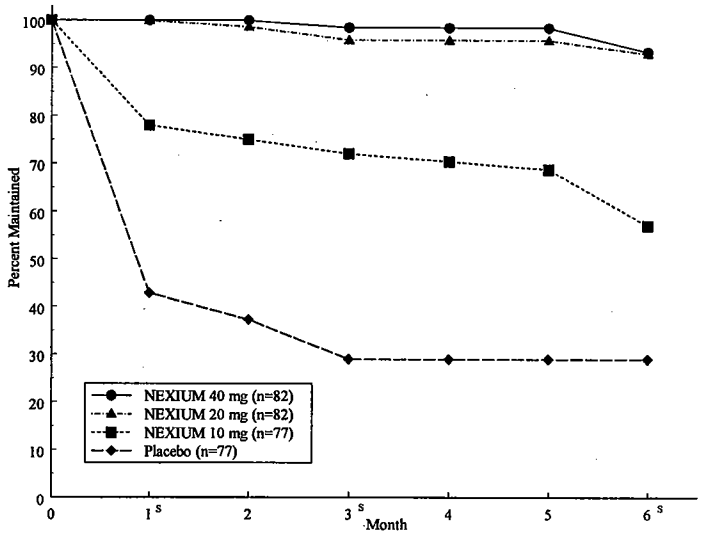
The percentage of patients that maintained healing of erosive esophagitis at the various time points are shown in the figures below:

Maintenance of Healing Rates by Month (Study 177)



s= scheduled visit

Maintenance of Healing Rates by Month (Study 178)



s= scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with NEXIUM compared to placebo. In both studies, the proportion of patients on NEXIUM who remained in remission and were free of heartburn and other GERD symptoms was well differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with NEXIUM 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

Symptomatic Gastroesophageal Reflux Disease (GERD)

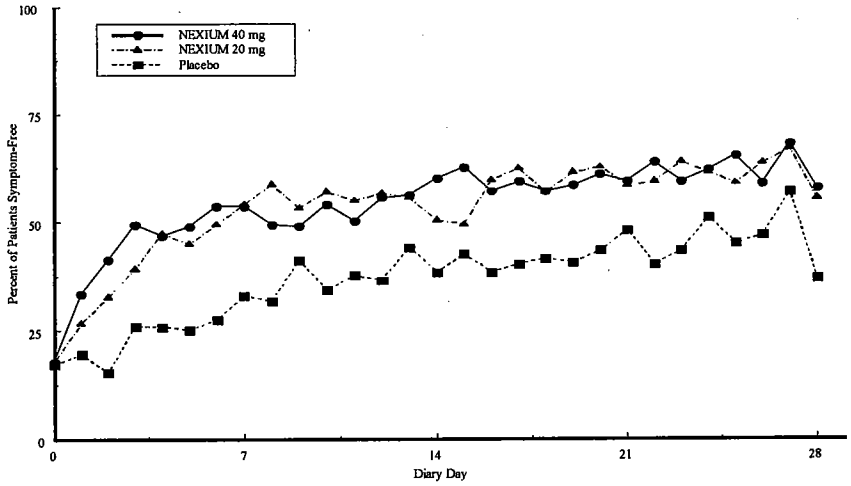
Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with NEXIUM 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the NEXIUM groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

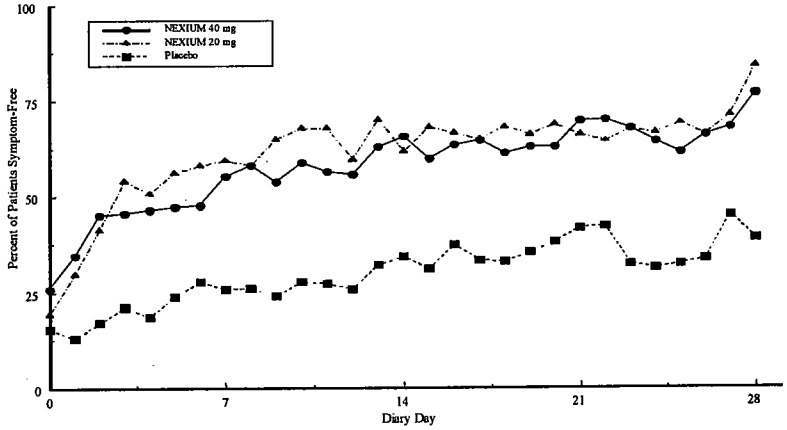
No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

The percent of patients symptom-free of heartburn by day are shown in the figures below:

Percent of Patients Symptom-Free of Heartburn by Day
(Study 225)



Percent of Patients Symptom-Free of Heartburn by Day (Study 226)



In three European symptomatic GERD trials, NEXIUM 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

Helicobacter pylori *(H. pylori) Eradication in Patients with Duodenal Ulcer Disease*

Triple Therapy (NEXIUM/amoxicillin/clarithromycin): Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NEXIUM 40 mg once daily plus clarithromycin 500 mg twice daily. The second study (193) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NEXIUM 40 mg once daily. *H. pylori* eradication rates, defined as at least two negative tests and no positive tests from CLOtest®, histology and/or culture, at 4 weeks post-therapy were significantly higher in the NEXIUM plus amoxicillin and clarithromycin group than in the NEXIUM plus clarithromycin or NEXIUM alone group. The results are shown in the following table:

***H. pylori* Eradication Rates at 4 Weeks after 10 Day Treatment Regimen**
% of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Treatment Group	Per-Protocol[†]	Intent-to-Treat [‡]
191	NEXIUM plus amoxicillin and clarithromycin	84%* [78, 89] (n=196)	77%* [71, 82] (n=233)
	NEXIUM plus clarithromycin	55% [48, 62] (n=187)	52% [45, 59] (n=215)
193	NEXIUM plus amoxicillin and clarithromycin	85%** [74, 93] (n=67)	78%** [67, 87] (n=74)
	NEXIUM	5% [0, 23] (n=22)	4% [0, 21] (n=24)

[†] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥ 0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the analysis as not *H. pylori* eradicated.
[‡] Patients were included in the analysis if they had documented *H. pylori* infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not *H. pylori* eradicated.
*$p < 0.05$ compared to NEXIUM plus clarithromycin
**$p < 0.05$ compared to NEXIUM alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the NEXIUM plus amoxicillin and clarithromycin group was 75% (n=156) and 57% (n=60) respectively, in the 191 and 193 studies (per-protocol analysis).

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

NEXIUM is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8-week course of NEXIUM may be considered.

Maintenance of Healing of Erosive Esophagitis

NEXIUM is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

NEXIUM is indicated for treatment of heartburn and other symptoms associated with GERD.

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

Triple Therapy (NEXIUM plus amoxicillin and clarithromycin): NEXIUM, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) 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.**)

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 **CLINICAL PHARMACOLOGY, Microbiology** and the clarithromycin package insert, **CLINICAL PHARMACOLOGY, Microbiology**.)

CONTRAINDICATIONS

NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

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

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

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

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.)

Amoxicillin: 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.

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.*

PRECAUTIONS

General

Symptomatic response to therapy with NEXIUM 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, of which NEXIUM is an enantiomer.

Information for Patients

Patients should be informed of the following:
NEXIUM Delayed-Release Capsules should be taken at least one hour before meals.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

Antacids may be used while taking NEXIUM.

Drug Interactions

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes

would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts and digoxin).

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Combination Therapy with Clarithromycin

Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics: Combination Therapy with Antimicrobials.)**

Concomitant administration of clarithromycin with pimozide is contraindicated. (See clarithromycin package insert.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) 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 (about 5.6 times the human dose on a body surface area basis) for 1 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 1 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. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 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.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.
The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and 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.

Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) 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 (about 5.5 to 56 times the human dose on a body surface area basis) 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 at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). There are no adequate and 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.

Amoxicillin

Pregnancy Category B. See full prescribing information for amoxicillin before using in pregnant women.

Clarithromycin

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

Nursing Mothers

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, 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.

Geriatric Use
Of the total number of patients who received NEXIUM in clinical trials, 778 were 65 to 74 years of age and 124 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,400 patients in the United States and over 2,600 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole.

Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system:

Body as a Whole: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; ***Cardiovascular***: flushing, hypertension, tachycardia; ***Endocrine***: goiter; ***Gastrointestinal***: bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; ***Hearing:*** earache, tinnitus; ***Hematologic***: anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; ***Hepatic***: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic/Nutritional:*** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; ***Musculoskeletal***: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; ***Nervous System/Psychiatric***: anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder,

somnolence, tremor, vertigo, visual field defect; ***Reproductive***: dysmenorrhea, menstrual disorder, vaginitis; ***Respiratory***: asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages***: acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; ***Special Senses:*** otitis media, parosmia, taste loss, taste perversion; ***Urogenital***: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; ***Visual***: conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Reports – There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports have included rare cases of anaphylactic reaction, severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis.

Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert, **ADVERSE REACTIONS** section.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with NEXIUM plus amoxicillin and clarithromycin, no adverse events peculiar to these drug combinations were observed. Adverse events that occurred have been limited to those that had been observed with either NEXIUM, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse events for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse events were observed at higher rates with triple therapy than were observed with NEXIUM alone.

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

Laboratory Events

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to NEXIUM, were reported in ≤ 1% of patients: increased creatinine, uric acid, total

bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone (see **CLINICAL PHARMACOLOGY**, *Endocrine Effects* for further information on thyroid effects). Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

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

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** section.

OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

There have been some reports of overdosage with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - **ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

DOSAGE AND ADMINISTRATION

The recommended adult dosages are outlined in the table below. NEXIUM Delayed-Release Capsules should be swallowed whole and taken at least one hour before eating.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

The pellets have also been shown *in vitro* to remain intact when exposed to tap water, orange juice, apple juice and yogurt.

Recommended Adult Dosage Schedule of NEXIUM

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily**
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
NEXIUM	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

*(see **CLINICAL STUDIES**). The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks of treatment may be considered.
**Controlled studies did not extend beyond six months.
***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

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

Special Populations

Geriatric: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Renal Insufficiency: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Hepatic Insufficiency: No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of NEXIUM should not be exceeded (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Gender: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

HOW SUPPLIED

NEXIUM Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and 20 mg in yellow on the body. They are supplied as follows:

NDC 0186-5020-31 unit of use bottles of 30
NDC 0186-5022-28 unit dose packages of 100
NDC 0186-5020-54 bottles of 90

NDC 0186-5020-82 bottles of 1000

NEXIUM Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and 40 mg in yellow on the body. They are supplied as follows:

NDC 0186-5040-31 unit of use bottles of 30
NDC 0186-5042-28 unit dose packages of 100
NDC 0186-5040-54 bottles of 90
NDC 0186-5040-82 bottles of 1000

Storage
Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature]. Keep container tightly closed. Dispense in a tight container if the product package is subdivided.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Fifth Edition: Approved Standard NCCLS Document M7-A5, Vol. 20, no. 2, NCCLS, Wayne, PA, January 2000.

Manufactured for:
AstraZeneca LP
Wilmington, DE 19850
By: AstraZeneca AB
Sodertalje, Sweden

Product of France

620514-~~04~~XX
9346~~04~~XX

Rev. ~~02/03~~ 10/03

AstraZeneca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-153/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-153/SLR-015

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

Sponsor: Astra Zeneca, LP

Material Reviewed

Submission Date(s): October 23, 2003

Receipt Date(s): October 23, 2003

Background and Summary Description

NDA 21-153 for Nexium® (esomeprazole) Delayed-Release Capsules was approved February 20, 2001. Please note that NDA 21-154 and NDA 21-153 were both approved on February 20, 2001. NDA 21-154 was acted on jointly with the Division of Special Pathogens and approved the use of Nexium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori.* Consequently, this NDA(21-153) is approved for the following indications: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; 3) treatment of symptomatic gastroesophageal reflux disease; and 4) the use of Nexium (esomeprazole magnesium) Delayed-Release Capsules in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

NDA 21-153/SLR-015 was submitted to incorporate wording that was requested by the Agency via a supplement request letter on November 4, 2002 that requested the following:

"Under the **ADVERSE REACTIONS, Postmarketing Reports** section of the package insert, add the following terms: 1) severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme; and 2) pancreatitis."

Consequently, NDA 21-153/SLR-015 provides for revisions to the Adverse Reactions, Postmarketing Reports section of the package insert.

Review

The proposed labeling (620514-XX, dated: 10/23/03, received: 10/23/03) was compared to the currently approved labeling (620514-05, S-011, dated: 03/17/03, received: 03/18/03, approved: 09/18/2003). All proposed changes were indicated in the sponsor's annotated proposed label. The proposed changes were as follows, and are noted by underline:

ADVERSE REACTIONS

The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,400 patients in the United States and over 2,600 patients in Europe and

Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole.

Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system:

***Body as a Whole*: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; *Cardiovascular*: flushing, hypertension, tachycardia; *Endocrine*: goiter; *Gastrointestinal*: bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; *Hearing:* earache, tinnitus; *Hematologic*: anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; *Hepatic*: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; *Metabolic/Nutritional:* glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; *Musculoskeletal*: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; *Nervous System/Psychiatric*: anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; *Reproductive*: dysmenorrhea, menstrual disorder, vaginitis; *Respiratory*: asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; *Skin and Appendages*: acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; *Special Senses:* otitis media, parosmia, taste loss, taste perversion; *Urogenital*: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; *Visual*: conjunctivitis, vision abnormal.**

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Reports – There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports have included rare cases of anaphylactic reaction, severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis.

Please note that the proposed changes are verbatim to those requested by the Agency in our November 4, 2002 supplement request letter (see attachment 1).

The proposed label has been reviewed by the Clinical Reviewer, Dr. Gail Moreschi. Dr. Moreschi found these changes acceptable in her review dated February 18, 2004 (see attachment 2).

Conclusions

1. The revised draft package insert submitted on October 23, 2003 is acceptable.
2. An approval letter should be sent to the sponsor.

Melissa Hancock Furness
Regulatory Project Manager, B.S.

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: MHF 04/10/04
Revised/Initialed: BS 04/14/04
Finalized: MHF 04/15/04
Filename: 04-2004 Nexium_PM_LabelingReview_N21153_S015

CSO LABELING REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-153

AstraZeneca LP
Attention: Michael Angioli
725 Chesterbrook Boulevard
Mailstop E-2C
Wayne, PA 19087-5677

Dear Mr. Angioli:

Please refer to your new drug application (NDA) for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We have recently evaluated postmarketing reports of serious adverse skin events and pancreatitis associated with the use of proton pump inhibitors and have determined that these adverse events should be reflected in the labeling for all proton pump inhibitors. Specifically, we noted 11 cases of serious adverse skin events and 9 cases of pancreatitis associated with the use of esomeprazole.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of Nexium (esomeprazole magnesium):

> Under the **ADVERSE REACTIONS, Postmarketing Reports** section of the package insert, add the following terms: 1) severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme; and 2) pancreatitis.

Please submit draft labeling as a prior approval supplement to this application and incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM

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

DATE: February 18, 2004

TO: NDA 21-153/S-015

FROM: Gail I. Moreschi, MD, MPH, FACP

SUBJECT: NDA 21-153/S-015, Nexium (esomeprazole magnesium) Delayed Release Capsules; Submission of October 23, 2003

This submission is a response by the applicant to the FDA's request, under the ADVERSE REACTIONS, Postmarketing Reports section to add the following terms: severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis.

The applicant has proposed an amendment to the package insert in this application. These changes are warnings about possible adverse reactions to Nexium.

The applicant has proposed the following changes in the label in an annotated version as shown below: ADDITIONS INDICATED BY DOUBLE UNDERLINING

Postmarketing Reports – There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports have included rare cases of anaphylactic reaction, severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis.

The proposed label change is acceptable. I recommend that this application be approved.

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/s/

Gail Moreschi
2/18/04 04:33:50 PM
MEDICAL OFFICER

Hugo Gallo Torres
2/18/04 08:07:22 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-153/S-015

PRIOR APPROVAL SUPPLEMENT

Astra Zeneca LP
Wilmington, DE 19803-8355
Attention: George Kummeth, Director Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

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

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

NDA Number: NDA 21-153

Supplement number: S-015

This supplemental application proposes the following: changes to the **Adverse Reactions, Postmarketing Commitments** section of the Nexium package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 22, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 24, 2004.

All communications concerning this supplement 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 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melissa Furness
2/10/04 06:30:15 PM