CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-810/S062

APPROVAL LETTER

NDA 19-810/S-062

FEB 23 2000

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

Dear Dr. Horowitz:

Please refer to your supplemental new drug application dated August 30, 1999, received August 31, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplemental new drug application provides for revision of the PRECAUTIONS section of the package insert to include a *Geriatric Use* subsection.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 30, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-810/S-062." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

/S/ 2-23-00

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

cc:
Archival NDA 19-810/SLR-062
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/S.Kress
H.Gallo-Torres
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HFD-820/DNDC Division Director
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APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-810/S062

FINAL PRINTED LABELING

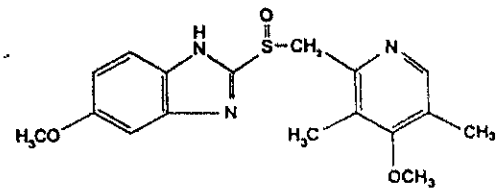
FEB 23 2000

08/23/99

Prilosec® *(omeprazole)*
DELAYED-RELEASE CAPSULES

DESCRIPTION

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



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

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

*Registered trademark of Astra AB

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

Pharmacokinetics: Combination Therapy with Antimicrobials

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

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

Clarithromycin Tissue Concentrations
2 hours after Dose[1]

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

[1] Mean ± SD (µg/g)

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

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

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

Pharmacodynamics

Mechanism of Action
Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

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

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

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

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

*Single Studies

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

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

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

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

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

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

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

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

Clinical Studies

Duodenal Ulcer Disease

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

Treatment of Active Duodenal Ulcer
% of Patients Healed

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

($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with PRILOSEC 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received PRILOSEC had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

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

Treatment of Active Duodenal Ulcer
% of Patients Healed

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

*(p < 0.01)

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

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

Treatment of Active Duodenal Ulcer
% of Patients Healed

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

*(p ≤ 0.01)

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

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

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

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

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

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

· ($p < 0.05$) versus clarithromycin plus amoxicillin.

Dual Therapy (PRILOSEC/clarithromycin)— Four randomized, double-blind, multi-center studies (M93-067, M93-100, M92-812b, and M93-058) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or by PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies M93-067 and M93-100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 228 patients in Study M93-100. These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies. Studies M92-812b and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in study M92-812b and 208 patients in Study M93-058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below. *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated of *H. pylori*. In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication because they were found to have an ulcer at the end of treatment.

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

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

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

[a] Statistically significantly higher than clarithromycin monotherapy ($p < 0.05$)
[b] Statistically significantly higher than omeprazole monotherapy ($p < 0.05$)

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

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

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

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

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

Gastric Ulcer

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

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

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

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

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

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

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

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

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

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

% Successful Symptomatic Outcome*

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

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

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

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

* ($p < 0.01$) PRILOSEC versus placebo

In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, PRILOSEC in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with PRILOSEC than in those taking placebo or histamine H_2- receptor antagonists.

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

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

Life Table Analysis

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

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

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

Life Table Analysis

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

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

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

Pathological Hypersecretory Conditions
In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

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

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

Helicobacter
Helicobacter pylori
Pretreatment Resistance
Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in

omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 μg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 μg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 μg/mL by Etest®.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

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

*Includes only patients with pretreatment clanthromycin susceptibility test results
*Susceptible (S) MIC ≤ 0.25 • g/mL, Intermediate (I) MIC 0.5 - 1.0 μg/mL, Resistant (R) MIC ≥ 2 μg/mL

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

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤

0.25 μg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*

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

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

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

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

[a]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	Clanthromycin	0.015 - 0.12 (μg/mL)
H. pylori ATCC 43504	Amoxicillin	0.015 - 0.12 (μg/mL)

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

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

INDICATIONS AND USAGE

Duodenal Ulcer

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

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

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

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

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

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

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

Erosive Esophagitis
PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

(See CLINICAL PHARMACOLOGY, Clinical Studies.)

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

Maintenance of Healing of Erosive Esophagitis
PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS

Clarithromycin
CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.** (See WARNINGS in prescribing information for amoxicillin.)

Antimicrobials

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

PRECAUTIONS

General

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

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

Information for Patients

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

Drug Interactions

Other

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical

reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC.

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still

showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

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

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

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

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during preg-nancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use
Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

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

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

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0 5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0 0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0 0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

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

Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3 3
Asthenia	1.3	0 8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10 0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

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

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

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

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

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This

finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

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

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain

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

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

Respiratory: Epistaxis, pharyngeal pain

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

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

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

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

Combination Therapy for H. pylori Eradication
In clinical trials using either dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin, and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that

have been previously reported with omeprazole, clarithromycin, or amoxicillin.

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

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

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

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of PRILOSEC is 20 mg once daily. Most patients heal within four weeks. Some patients may

require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

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

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

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNING, and for information regarding dosing in elderly and renally impaired patients (PRECAUTIONS: General, PRECAUTIONS: Geriatric Use and PRECAUTIONS: Drug Interactions).

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

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

Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE.)

Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

Pathological Hypersecretory Conditions
The dosage of PRILOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day.

Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years.

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

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

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

HOW SUPPLIED

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

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

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

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

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

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

Storage

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

Issued

Manufactured by:
Merck & Co., Inc., West Point, PA 19486
Distributed by:

ASTRA Astra Pharmaceuticals, L.P., Wayne, PA 19087

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-810/S062

MEDICAL REVIEW(S)

JAN - 5 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA:	19-810 SLR-062
Applicant:	AstraZeneca LP
Drug Name:	Prilosec® (Omeprazole) Delayed-Release Capsules
Indication:	***Geriatric Use*** Labeling Supplement
Date submitted:	August 30, 1999
Date received by Medical Officer:	September 10, 1999
Review completed:	January 4, 2000
Reviewer:	Scheldon Kress, M.D.

Introduction

The sponsor presented data summarizing information on the safety and efficacy of omeprazole administered to geriatric patients in controlled clinical trials as well as safety information gathered through post-marketing surveillance to support proposed ***Geriatric Use*** labeling.

Introduction to Safety Data
The safety profile of omeprazole in the geriatric population is supported by data from the U.S. Merck Research Laboratories, Astra Merck Inc., and [redacted] marketing applications, the non-U.S. marketing applications sponsored by Astra Hässle, and the data from post-marketing surveillance.

The application reviewed the incidence of clinical adverse experiences and serious adverse experiences in relation to the age of study patients.

For the marketing applications included in this review the general definitions of an adverse event are as follows:

An adverse event (AE) is any unfavorable and unintended change in the:

- structure (signs)
- function (symptoms)
- chemistry (laboratory data)

of the body temporally associated with any use of a test substance in humans, whether or not considered related to the use of the test substance.

A serious adverse event (SAE) is an adverse event which constitutes a definite hazard or handicap to the patient (or offspring) including, but not limited to, an AE which results in:

- death
- permanent or significant disability
- in-patient hospitalization or prolongation of existing in-patient hospitalization
- life-threatening
- congenital anomaly
- cancer

Any AE fulfilling these criteria is serious even if it is the result of an overdose, interaction or drug abuse.

Applicable Regulatory Paragraphs

The labeling is being revised under the applicable proposed labeling revision paragraph: 21CFR §201.57(f)(10) Geriatric Use.

21CFR §201.57(f)(10)(ii)(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "**Geriatric** use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), -- percent were 65 and over, while –percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, 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.

Geriatric Population Safety in Omeprazole Clinical Trials

Omeprazole is indicated for the short-term treatment of active duodenal ulcer, active gastric ulcer, symptomatic GERD, erosive esophagitis, and *Helicobacter pylori*.

Omeprazole is indicated for longer-term treatment (more than 12 weeks) of the following disorders:

- maintenance treatment of erosive esophagitis
- pathological hypersecretory disorders

The sponsor reviewed a total of thirty-eight (38) clinical trials that included a total of two-thousand seven hundred and eighty-five (2785) patients over the age of 65 who received omeprazole and were analyzed for safety. Within each marketing application,

the adverse event experience was compared in younger (<65 years of age) and elderly (>65 years of age) patients.

This application requests specific approval of omeprazole usage in the geriatric population. Safety issues become more of a major health concern when drugs are administered to the elderly. Often drugs are taken in combination with many other drugs at a time when metabolic function of the liver and kidneys is declining. Since the efficacy of this drug has been reviewed under multiple prior NDAs, this medical reviewer has chosen to concentrate on those studies dealing with the safety of this drug when administered to patients 65 years of age or older and for longer than 12 weeks. If safety issues do exist, signals for significant adverse events are more likely to be detected among this group of subjects.

Geriatric Safety in Omeprazole Clinical Trials of Greater Than 12 Weeks

The following table presents those patients age 65 or older who participated in clinical trials lasting 6 months or longer for which adverse events were evaluated and compared to their frequency among patients < 65 years of age. Most patients received omeprazole in doses ranging from 10 mg to 40 mg per day for long term management of reflux esophagitis and duodenal ulcer. Those 147 patients in studies I-627, I-568/569, and I-581 were given omeprazole 20 mg daily as weekend therapy (three times per week).

Table 1
Patients z65 Years of Age
Participating in Omeprazole Studies for At Least 6 Months

Study Number	Therapeutic Indications	Duration of Therapy	Number Patients z65	Adverse Events Among Elderly Omeprazole Treated Patients
010	Maintenance of healing of erosive esophagitis	6 Months	58	Diarrhea slightly higher
I-621	Maintenance treatment of erosive esophagitis	12 Months	94	The most common AEs in the age group < 65 years were diarrhea, headache, flatulence, and viral infection; in the age group > 65 years were diarrhea and dizziness/vertigo: in the age group >74 years were fracture, bronchitis, diarrhea, and pain. Overall, AEs were reported at about the same frequency for all three age groups. Three patients reported 5 SAEs possibly related to omeprazole treatment. An 81-year old patient with biliary cirrhosis and hypertension suffered a stroke and severe panmyelophthisis. Headache was reported in two younger patients. A 31-year old reported moderate headache (migraine) and hypertension, and a 58 year old reported headache Twelve patients died during/after daily treatment with omeprazole, and one patient during week-end treatment. None of the AEs were considered causally related to omeprazole treatment by the investigator.
I-613	Treatment of erosive esophagitis		21	
I-548/ I-614	Treatment of peptic ulcer or erosive esophagitis	1+ Years	208	
I-565-01	Treatment of peptic ulcer or esophagitis	5 Years	16	
I-565-15	Treatment of peptic ulcer or esophagitis	2-3 Years	12	
I-627	Treatment of erosive/ ulcerative esophagitis	6+ Months	67	The most common AEs occurring with a frequency of at least 2% in the age group below 65 years were epigastric pain, diarrhea and back pain. In patients z65 years of age, abdominal pain, epigastric pain, constipation, nausea, flatulence, hypertension, increased alkaline phosphatase were reported most frequently. There was no substantial difference in the AE frequencies between the younger and the older age groups. Six patients reported 8 SAEs with a possible causal relationship to omeprazole treatment. One 27-year-old patient experienced abdominal pain after meals, while another 27-year-old patient experienced an asthmatic attack of sudden onset. An 83-year-old patient was diagnosed with tubulo-interstitial nephritis possibly related to both omeprazole and concurrent erythromycin therapy. A 52-year-old patient developed urticaria, pruritis and Quincke's oedema. A 62-year-old patient experienced an acute psychosis. A 77-year-old patient died of sudden syncope. Fifteen patients, including 8 patients <65 and 7 patients z65 of age died during/after daily treatment with omeprazole. None of the AEs resulting in death were considered causally related to omeprazole treatment by the investigator.
I-640	Treatment of esophagitis	6+ Months	105	
I-641	Treatment of reflux esophagitis	12+ Months	199	
I-568/ 569	Treatment duodenal Ulcers	6 Months	112	
I-581	Treatment duodenal Ulcers	6+ Months	20	
I-900	Treatment and prevention of duodenal ulcers	6+ Months	266	
I-901	Treatment and prevention of duodenal ulcers	12+ Months	28	
		Total ->	**1206**	

The most common adverse events by age group during long term management of reflux esophagitis and prevention of relapse in duodenal ulcer are presented in Table 2 (sponsor's Table 21).

Table 2
Most Common Adverse Events by Age Group During Long Term Management of Reflux Oesophagitis and Prevention of Relapse in Duodenal Ulcer

Drug	Omeprazole	Omeprazole
Age	< 65	≥ 65
No of patients	954	272
No (%) of patients with AE:	347 (36.4)	116 (42.6)
Epigastric pain	29 (3.0)	9 (3.3)
Diarrhea	29 (3.0)	4 (1.5)
Abdominal pain	18 (1.9)	10 (3.7)
Nausea	18 (1.9)	7 (2.6)
Back pain	24 (2.5)	0
Flatulence	16 (1.7)	7 (2.6)
Weight increase	17 (1.8)	5 (1.8)
Hypertension	14 (1.5)	7 (2.6)
Respiratory infection	17 (1.8)	4 (1.5)
SGPT increased	17 (1.8)	4 (1.5)
Fatique	15 (1.6)	4 (1.5)
Vomiting	13 (1.4)	5 (1.8)
Headache	15 (1.6)	2 (0.7)
Chest pain	13 (1.4)	3 (1.1)
Constipation	8 (0.8)	8 (2.9)
Accident and/or injury	11 (1.2)	3 (1.1)
Dizziness/vertigo	13 (1.4)	1 (0.4)
Phosphatase alkaline increased	5 (0.5)	7 (2.6)

The most common AEs occurring with a frequency of at least 2% in the age group below 65 years were epigastric pain, diarrhea and back pain. In patients ≥ 65 years of age abdominal pain, epigastric pain, constipation, nausea, flatulence, hypertension, and increased alkaline phosphatase were reported most frequently. There was no substantial difference in the AE frequencies between the younger and older age groups.

Geriatric Safety in Omeprazole Clinical Trials in Patients Taking NSAIDs

The sponsor summarized a series of clinical studies on the safety and tolerability of omeprazole in patients at risk of gastric and/or duodenal lesions associated with non-steroidal anti-inflammatory drug treatment.

- Healing phase Studies B1 – B2 compared omeprazole 20 mg and 40 mg QD with ranitidine or misoprostol during a 4–8 week treatment period
- Prophylaxis phase Studies B1 – B4 compared omeprazole 20 mg QD with ranitidine, misoprostol and placebo during 3–6 months of treatment.

Adverse events were reported at relatively high frequencies in all groups (53-68%) in the healing studies. The number of AE reported for omeprazole, ranitidine and placebo were rather similar (53-56%). A total of 440 patients aged ≥65 were included in these studies. There were no age-related differences in the frequency of AEs reported during both phases of the omeprazole treated patients.

Adverse Experiences Reported in U.S. Marketing Applications

In 1988 in the medical officer review of the original NDA 19-810, Dr. Hugo Gallo-Torres, analyzed the AEs reported on 297 patients ≥ 65 years of age from a total of 1771 patients. He concluded that the percent of elderly patients enrolled in ——— sponsored studies who had at least one clinical adverse experience was similar to that of subjects under 65 years of age in both Merck- and Hässle-sponsored trials. Sixty-nine deaths occurred before the cutoff date (7/2/1987) in the worldwide population (N=9000) of all patients (included 41 aged < 65 and 26 aged ≥ 65 years of age) exposed to omeprazole treatment. None of these deaths were considered causally related to omeprazole treatment.

In 1993 in the safety review of NDA 19-810 SE-019, 158 deaths were reported as of September 30, 1992 among patients taking omeprazole. All deaths were reviewed as to their relationship to the study drug. Only 7 were considered related to omeprazole (2 related, 3 possibly related, 2 probably related, and 0 definitely related) by the investigators. Review of all of these 7 deaths by this medical officer finds that while there may have been a temporal relationship between the deaths and the study drug, there is no pattern or evidence to suggest that omeprazole was responsible for these deaths.

Post Marketing Surveillance

The sponsors evaluated the safety profile of omeprazole utilizing data from the post-marketing surveillance. AstraZeneca LP received reports of possible adverse events related to omeprazole exposure via three principal ways:

- direct reports to the company from individual doctors
- reports to the company by the national regulatory agencies
- publication in medical journals

AstraZeneca LP maintains a database of all spontaneous reports of possible adverse events associated with omeprazole. All reports are retained including those cases in which a causal relation with omeprazole seems unlikely. The total number of reports of possible adverse events by system organ class for all patients and for geriatric patients (≥65 years of age) treated with omeprazole, and the ratio of adverse events in geriatric population are presented in Table 3 (sponsor's Table 22).

Table 3

Ratio of Adverse Event Reports in Geriatric Patients to All Patients Treated with Omeprazole in Post-Marketing Surveillance

System Organ Class	No of AEs		Ratio of AEs in Geriatric Patients
	Geriatric Patients	All Patients	
Application Site Disorder	4	9	44.4
Body as a Whole - General Disorders	1281	4230	30.3
Cardiovascular Disorders, General	216	426	50.7
Central and Peripheral Nervous System Disorder	470	1687	27.9
Collagen Disorders	13	49	26.5
Endocrine Disorders	37	131	28.2
Foetal Disorders	3	41	7.3
Gastro-Intestinal System Disorders	1282	4039	31.7
Hearing and Vestibular Disorders	36	152	23.7
Heart Rate and Rhythm Disorders	132	373	35.4
Liver and Biliary System Disorders	166	649	25.6
Metabolic and Nutritional Disorders	244	830	29.4
Musculo-Skeletal System Disorders	220	698	31.5
Myo-, Endo-, Pericardial and Valve Disorders	152	277	54.9
Neonatal and Infancty Disorders	0	13	0
Neoplasms	250	630	39.7
Platelet, Bleeding and Clotting Disorders	117	345	33.9
Psychiatric Disorders	377	1404	26.9
Red Blood Cell Disorders	124	293	42.3
Reproductive Disorders, Female	34	144	23.6
Reproductive Disorders, Male	23	105	21.9
Resistance Mechanism Disorders	109	320	34.1
Respiratory System Disorders	366	852	43
Skin and Appendages Disorders	478	1542	31
Special Senses Other, Disorders	45	154	29.2
Urinary System Disorders	214	535	40
Vascular (Extracardiac) Disorders	189	384	49.2
Vision Disorders	85	290	29.3
White Cell and Resistance Disorders	73	192	38

Safety information provided in the spontaneous reports can be interpreted in the context of omeprazole use in the general population. The annual numbers of omeprazole use in three age groups (patients < 65, 65-74, and >75 years of age) estimated by _____ are presented in Table 4 (sponsor's Table 23) and in Table 5 (a July 22,1999 update also supplied by _____

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Table 4
Omeprazole-Drug Appearances by Patient Age (Thousands)

Year/ Share	1993	Share	1994	Share	1995	Share
TOTAL						
less than 65						
age 65-74						
older than 75						
Year/ Share						
TOTAL						
less than 65						
age 65-74						
older than 75						

Table 5
Annual Numbers of Omeprazole Use by Age Group
(update supplied by)

Drug Appearances by Patient Age (Thousands)												
	1993	Share	1994	Share	1995	Share	1996	Share	1997	Share	1998	Share
PRILOSEC												
less than 65												
age 65-74												
older than 75												

These estimates of omeprazole use have certain limitations:

- These data are based on a panel of 3540 physicians. This sample represents 1 percent of the covered physicians and therefore, the data have a large projection factor and confidence intervals.

- Drug Appearances are recommendations by the physician to the patient. It does not necessarily mean that the patient had the prescription filled or that Prilosec was the product dispensed.

Besides these limitations, this analysis provides a considerable amount of useful information on omeprazole use for the years 1993 through 1998. Through these years, geriatric patients (≥65 years of age) had approximately ——— share in omeprazole use, but the over 65 years of age users showed an annual ———————; percentage as users of omeprazole.

This estimate of omeprazole use in different age groups can be used in the evaluation of adverse event frequencies in different segments of the patient population. A consequence of this approach is the focus on adverse events that occur in the given age group at a higher rate than the share of omeprazole use for this age group. Thus the evaluation of adverse events in the geriatric population may focus on adverse events that occur with the rate of over ——

There are few categories of adverse events with a ratio higher than ——in geriatric patients: myo-, endo-, pericardial and valve disorders ———, general cardiovascular disorders ——— vascular (extracardiac) disorders ——— application site disorders ———, respiratory system disorders ——— urinary system disorders ——— red blood cell disorders ———, and neoplasms ———

Cardiovascular adverse events occurred with the highest rate in the geriatric patients. Myo-, endo-, pericardial and valve disorders category included a high incidence and a higher ratio in the elderly of angina pectoris, coronary artery disease, myocardial infarction, and heart attack. General cardiovascular disorders included a high incidence of the following conditions: high blood pressure, aneurysm, cardiac failure, circulatory failure, congestive failure, and syncope, while the vascular (extracardiac) disorders included cerebrovascular disorder and pulmonary infarction. These types of events are generally predictable to occur with a higher frequency in this age group. The elderly are particularly vulnerable to degenerative cardiovascular diseases and cardiovascular adverse events.

Likewise, neoplasms, urinary system disorders, respiratory system disorders and an assortment of anemias are generally predictable to occur with a higher frequency in this age group. The elderly are particularly vulnerable to a wide variety of degenerative diseases and symptoms presenting as possible adverse events. These should not present a limitation to the use of omeprazole in geriatric patients.

Adverse Events from Search of Medical Literature

Medline search on 12/15/99 for PRILOSEC/adverse effects or Omeprazole/adverse effects in aged (over 65) for last 10 years fielded 208 citations. No reference articles were found that dealt specifically with adverse events among omeprazole users over age 65.

Sponsors Conclusions on Safety

This review of the safety profile of omeprazole is based on information from international and domestic studies including approximately 7700 patients < 65 years of age and 2200 patients > 65 years of age.

Overall, there were no substantial, clinically significant differences in the occurrence rate and pattern of AEs between the younger and older age groups, based on medical reviews, attributable to treatment with omeprazole.

The most common AEs: diarrhea, headache, abdominal pain, and respiratory infection, were reported at approximately the same frequency in both age groups (< 65 and > 65 years of age) in different studies. There is no apparent age-related trend in the occurrence of the other frequent AEs: nausea, dizziness, constipation, and flatulence. Among patients ≥75 years of age diarrhea, fracture, and pain were the most common AEs.

Any differences in the frequencies of reported AEs in different age groups were not consistent across all studies. The percentages of patients reporting AEs with possible causal relationship to omeprazole treatment were similar across age groups.

The most commonly reported AEs in the geriatric population are comparable to those reported in the current labeling, and no data have emerged indicating that omeprazole is tolerated differently in younger and older patients.

Analyses of Efficacy Data in the Geriatric Population in Omeprazole Clinical Trials

Efficacy of omeprazole in the elderly population has been assessed using data from the U.S. Merck Research Laboratories (MRL), Astra Merck Inc., and _____ marketing applications, and non-U.S. marketing applications sponsored by Astra Hassle (Hassle).

The sponsor's report reviews efficacy parameters in relation to age of patients as presented in the clinical study reports included in the following U.S. marketing applications:

- Original NDA 19-810 for Prilosec Delayed-Release Capsules (December 21, 1987)
- Supplemental NDA 19-810/S-019 – Maintenance of Healing of Erosive Esophagitis (May 26, 1993)
- Supplemental NDA 19-810/S-033 – Active Benign Gastric Ulcer – (December 22,1994)
- Supplemental NDA 19-810/S-037 – Omeprazole Plus Clarithromycin – Eradication of *H. pylori* for the reduction of the risk of duodenal ulcer recurrence

- Supplemental NDA 19-810/S-055 – Omeprazole plus Clarithromycin plus Amoxicillin-Eradication of *H. pylori* for the reduction of the risk of duodenal ulcer recurrence

- Original NDA 19-810/General Correspondence – Treatment of Symptomatic GERD

- Supplemental NDA 19-810/S-002 – Short-Term Treatment of Active Duodenal Ulcer

Within these reports treatment efficacy of omeprazole was most often compared in younger (< 60 years of age) and elderly (≥60 years of age) patients. In some of these reports, the elderly group was defined as patients > 65 years of age and the younger age group was composed of patients ≤ 65 years of age.

Supplemental NDA 19-810/S033 – Active Benign Gastric Ulcer

This section summarizes efficacy data by age group in clinical studies associated with the use of omeprazole in the short-term treatment of gastric ulcers. Table 6 (sponsor's Table 27) tabulates the efficacy results for omeprazole treated patients reported in the five studies included in this supplement.

Table 6

Ulcer Healing Rates - Per-Protocol Analysis [a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
13	O 20 mg	8 weeks	Ulcer healing rates	< 60	115	77% healed
				≥ 60	76	87% healed
	O 40 mg			< 60	116	86% healed
				≥ 60	84	90% healed
I-505	O 30 mg	6 weeks	Ulcer healing rates	< 60	40	88% healed
				≥ 60	30	90% healed
I-524	O 20 mg	8 weeks	Ulcer healing rates	< 60	45	98% healed
				≥ 60	41	90% healed
I-555	O 20 mg	8 weeks	Ulcer healing rates	< 60	104	88% healed
				≥ 60	68	90% healed
	O 40 mg			< 60	96	94% healed
				≥ 60	75	99% healed
I-561	O 20 mg	8 weeks	Ulcer healing rates	< 60	52	100% healed
				≥ 60	22	86% healed

[a] Per-protocol patient population excluded patients with protocol violations.

In 3 studies, (Studies I-505, I-524, and I-555) there was no evidence of difference in efficacy in patients 60 years of age or older compared with patients younger than 60 years of age. In Study I-561, patients 60 years of age and older had slightly lower ulcer healing rates compared to patients younger than 60 years of age. In Study I-013, the sponsor by using logistic regression, found that age had a statistically significant influence on the healing rate. Older patients at the end of the study had higher healing rates.

As seen in Table 6, ulcer healing rates in patients 60 years of age and older, treated with omeprazole 20 mg QD, were numerically higher than in those patients younger than 60 years of age.

Supplemental NDA 19-810/S-037 Omeprazole plus Clarithromycin – Eradication of *H. pylori* for the Reduction of the Risk of Duodenal Ulcer Recurrence

This section summarizes efficacy data by age group in clinical studies with the use of omeprazole in the treatment of patients with duodenal ulcer. Table 7 (sponsor's Table 28) tabulates the efficacy results for omeprazole treated patients reported in the four studies included in this supplement.

The objective of Study M93-067 and M93-100 was to assess the efficacy of dual therapy with omeprazole and clarithromycin (O + C) to omeprazole monotherapy (O) and to clarithromycin monotherapy for healing and reducing recurrence of duodenal ulcers and the eradication of *H. pylori* from the gastric mucosa.

The objective of Study M92-812b and M93-058 was to compare the efficacy of dual therapy with omeprazole/clarithromycin (O + C) to that of monotherapy with omeprazole (O) for healing and reducing recurrence of duodenal ulcers and the eradication of *H. pylori* from the gastric mucosa.

In all 4 studies, enrolled patients had active duodenal ulcer(s) and *H. pylori* infection.

Table 7

Ulcer Healing and Eradication Rates of *H. pylori* - Evaluable Patients[a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
M92-812b	O + C	6 months	Ulcer prevalence	≤ 65	49	2% prevalence
				> 65	4	25% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	56	84% eradicated
				> 65	4	75% eradicated
	O	6 months	Ulcer prevalence	≤ 65	58	53% prevalence
				> 65	8	63% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	66	2% eradicated
				> 65	8	0% eradicated
M93-067	O + C	6 months	Ulcer prevalence	≤ 65	43	51% prevalence
				> 65	7	57% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	52	71% eradicated
				> 65	9	88% eradicated
	O	6 months	Ulcer prevalence	≤ 65	50	76% prevalence
				> 65	6	50% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	56	0% eradicated
				> 65	8	0% eradicated
M93-100	O + C	6 months	Ulcer prevalence	≤ 65	47	32% prevalence
				> 65	9	22% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	51	75% eradicated
				> 65	11	82% eradicated
	O	6 months	Ulcer prevalence	≤ 65	56	75% prevalence
				> 65	5	100% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	64	16% eradicated
				> 65	4	25% eradicated
M93-058	O + C	6 months	Ulcer prevalence	≤ 65	67	13% prevalence
				> 65	8	0% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	77	74% eradicated
				> 65	9	78% eradicated
	O	6 months	Ulcer prevalence	≤ 65	74	57% prevalence
				> 65	6	33% prevalence
		4 to 6 weeks	*H. pylori* Eradication	≤ 65	84	1% eradicated
				> 65	6	0% eradicated

[a] Evaluable patients met the evaluable criteria for the specific visit.

No overall differences were detected in any of the 4 studies on ulcer prevalence rates and *H. pylori* eradication rates in patients older than 65 years of age compared to patients 65 years of age and younger. Patients randomized to omeprazole/clarithromycin who were older than 65 years of age had moderately higher prevalence rates than patients 65 years of age and younger in Study M92-812b and moderately lower prevalence rates in Study M93-058. While patients randomized to omeprazole monotherapy who were older than 65 years of age had moderately higher prevalence rates compared to patients 65 years and younger in Study M93-100 and moderately lower prevalence rates in Study M93-058 and M93-067.

Patients randomized to omeprazole/clarithromycin who were older than 65 years of age had slightly higher eradication rates than patients 65 years of age and younger in Study M93-067. In Study M92-812b and M93-058, the sponsor found that no statistical significance was detected by the Breslow-Day test performed to test homogeneity of treatment differences across age.

For all 4 studies, additional analyses were also performed on other patient populations (Intent-to-Treat) and secondary objectives. There was no difference in efficacy detected between these two age groups in these other analyses.

Supplemental NDA 19-810/S-055 Omeprazole plus Clarithromycin plus Amoxicillin – Eradication of *H. pylori* for the reduction of the Risk of Duodenal Ulcer Recurrence

This section summarizes efficacy data by age group in clinical studies with the use of omeprazole plus amoxicillin and clarithromycin for the eradication of *H. pylori* infection in duodenal ulcer disease. Table 8 (sponsor's Table 31) tabulates the efficacy results reported in the three studies included in this supplement.

The objective of Studies 126, 127, and M96-446, were to evaluate the effects of combination therapy with omeprazole, amoxicillin, and clarithromycin (O + A + C) compared to combination therapy with clarithromycin and amoxicillin on eradication of *Helicobacter pylori.*

In Study 126 and 127, enrolled patients had one or more active duodenal ulcer(s) and *H.pylori* infection. The primary objective was to assess the efficacy of a ten-day treatment regimen of omeprazole/amoxicillin/clarithromycin followed by 10 days of omeprazole 20 mg QD on eradication of *H. pylori*. While in study M96-446, enrolled patients had an *H. pylori* infection and a history of duodenal ulcer with no active duodenal ulcer, gastric ulcer, duodenal erosions, or erosive esophagitis. The primary objective was to assess the efficacy of a ten-day treatment regimen of omeprazole/ amoxicillin/clarithromycin on eradication of *H. pylori.*

Efficacy results for omeprazole treated patients are presented in Table 8.

Table 8

Eradication Rates of *H. pylori*
Per-Protocol Analysis [a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
126	O + A +C	8 weeks	*H. pylori* Eradication	≤ 65	58	76% eradication
				> 65	5	100% eradication
127	O + A + C	8 weeks	*H. pylori* Eradication	≤ 65	52	85% eradication
				> 65	9	78% eradication
M96-446	O + A + C	4 to 6 weeks	*H. pylori* Eradication	< 65	54	89% eradication
				≥ 65	15	93% eradication

[a] Per-protocol patient population excluded patients with protocol violations

In Study 126 and 127, no overall difference in efficacy was observed in patients older than 65 years of age compared to patients 65 and younger. The sponsor using logistic regression, determined that age had no significant effect on H. pylori eradication rates at Week 8. In Study 126, patients older than 65 years of age, had slightly higher eradication rates than patients 65 years of age and younger.

Similarly, in Study M96-446, no difference in efficacy was observed in patients 65 years of age or older compared to patients younger than 65 years of age, as seen in Table 8.

For all 3 studies, additional analyses were also performed on other patient populations (Intent-to-Treat) and secondary objectives. There were no overall differences in efficacy detected between these two age groups in these other analyses.

Supplemental NDA 19-810/S-019 – Maintenance of Healing of Erosive Esophagitis

This section summarizes efficacy data by age group in clinical studies with the use of omeprazole in the continuing treatment of patients with healed erosive esophagitis obtained in 1 US study, 010, and 2 non-US studies, I-640 and I-641.

The objective for Study I-641 was to compare the recurrence of reflux symptoms following healing in patients with erosive/ ulcerative esophagitis, during a 12 month maintenance treatment period with omeprazole 20 mg QD, omeprazole 10 mg QD, or ranitadine 150 mg BID.

The objective for Study I-640 was to compare the recurrence of esophagitis during a 6 month maintenance treatment with omeprazole 20 mg QD, omeprazole 10 mg QD, or

placebo in patients with healed reflux esophagitis after treatment for 4 to 12 weeks with omeprazole 20 mg or omeprazole 40 mg QD.

Study 010 was designed to evaluate the effects of omeprazole 20 mg QD or omeprazole 20 mg 3 of 7 days as compared to placebo during 6 months of continuous treatment of patients with healed erosive esophagitis following treatment with 4 to 8 weeks of omeprazole 40 mg QD.

Table 9 (sponsor's Table 33) tabulates the efficacy results reported for omeprazole treated patients.

Table 9

Maintenance of Healing of Erosive Esophagitis - Per-Protocol Analysis[a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
010	O 20 mg od	6 months	Maintenance of healing of erosive esophagitis	< 60	84	80% healed
				≥ 60	40	75% healed
	O 20 mg 3 of 7 days	6 months		< 60	71	48% healed
				≥ 60	41	41% healed

[a] Per-protocol patient population excluded patients with protocol violations.

For Study I-641, during the maintenance phase, the sponsor performed regression analysis with age as one of the preliminary main effects. Age was included in the final model and was considered non-significant.

For Study I-640, the sponsor performed regression analysis with age as one of the preliminary effects. During the healing phase, age was determined to be non-significant and was excluded from the final model. However, during the maintenance phase, low age may have given positive contributions to the odds for staying in remission (p-value = 0.11).

For Study 010, the sponsor determined that age had no effect on treatment differences and was found to have no statistically significant relationship to relapse. They found no evidence of a decrease in efficacy in patients 60 years of age or older.

Supplement NDA 19-910/S-002 – Short-Term Treatment of Active Duodenal Ulcer

This section summarizes efficacy data by age group in Clinical Study 002 associated with the use of omeprazole in the short-term treatment of duodenal ulcer. Table 10 (sponsor's Table 35) presents the efficacy results for omeprazole treated patients.

Table 10

Ulcer Healing Rates - Per-Protocol Analysis [a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
002	O 20 mg	4 weeks	Ulcer healing rates	< 60 ≥ 60	109 36	83% healed 89% healed

[a] Per-Protocol patient population excluded patients with protocol violations.

No difference in efficacy was detected in omeprazole treated patients 60 years of age or older compared to patients younger than 60 years of age.

Original NDA 19-810 Short Term Treatment of Erosive Esophagitis

This section summarizes efficacy data by age group in clinical studies associated with the use of omeprazole in the short-term treatment of erosive esophagitis. Study 005 was designed to study the effects of omeprazole 20 mg and 40 mg as compared to placebo in the healing and symptomatic relief of patients with moderate to severe esophagitis. Table 11 (sponsor's Table 37) presents the efficacy results for omeprazole treated patients.

Table 11

Erosive Esophagitis Healing Rates - Per-Protocol Analysis [a]

Study Number	Treatment Group	Treatment Evaluation	Indication	Age Group	N	Results
005	O 20 mg	8 weeks	Erosive Esophagitis	< 60	46	78% healed
				≥ 60	37	76% healed
	Ome 40 mg			< 60	64	78% healed
				≥ 60	23	87% healed

[a] Per-Protocol patient population excluded patients with protocol violations.

In Study 005, no difference in efficacy was detected in patients 60 years of age or older compared to patients younger than 60 years of age. Using regression analysis, the sponsor found no prevailing difference between the omeprazole treated groups and placebo regardless of age.

Original NDA 19-810/General Correspondence – Treatment of Symptomatic GERD

This section summarizes efficacy data by age group in Clinical Study 037 associated with the use of omeprazole in the treatment of symptomatic GERD. Study 037 was designed to analyze the efficacy of omeprazole 10 mg and 20 mg Qd to relieve heartburn in patients with pathologic GERD without erosive esophagitis. Patients were randomly assigned to three treatment regimens: omeprazole 10 mg, 20 mg and placebo. in the healing and symptomatic relief of patients with moderate to severe esophagitis.

The sponsor detected numerical differences between patients 65 years of age and older compared to patients younger than 65. Using logistic regression, age was not found to be statistically significant influence on the overall success rates at the last week of evaluation. Generalized estimating equation (GEE) models were used to analyze the odds of daily (24 hour) heartburn relief over time. Age was determined to not effect the odds of having no heartburn.

Sponsor's Conclusions on Efficacy

This review of efficacy of omeprazole treatment in the geriatric population is based on information from domestic and international studies including a total of 4017 patients, of which 959 were 65 years of age and older. Some of the clinical studies analyzed the older population in patients 60 years of age and older instead of 65 years of age and older.

Overall, there is no evidence of a difference in effectiveness of omeprazole treatment in patients in the different age groups.

REVIEWER COMMENTS REGARDING GERIATRIC USE LABELING

This reviewer uncovered no data to question the safety of omeprazole among the elderly, ≥ 65 years of age. Based on extensive review of the clinical studies provided, there is no age-related trend in the occurrence rate and pattern of adverse events attributable to treatment with omeprazole.

Likewise, there is no evidence of a difference in therapeutic effectiveness of omeprazole treatment in patients 65 years of age or older compared to those less than 65 years of age.

Proposed Modifications to Existing Labeling:

The sponsor proposes the following addition to the existing labeling:

Geriatric Use
Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

This revision is acceptable

Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater potential exists for adverse events among those elderly with impaired renal and/or hepatic function.

In conclusion, the available data supplied by the sponsor in NDA 19-810 SLR-062 demonstrate compliance with paragraph: 21CFR §201.57(f)(10), information in the "Geriatric Use" subsection. The information provided by the sponsor fulfills the applicable requirements of paragraph 21CFR §201.57(f)(10)(ii)(B), [Standard language for paragraph (ii) labeling if the clinical studies did include a sufficient number of geriatric subjects to determine whether elderly respond differently and no difference in response was detected].

This medical officer recommends acceptance of the proposed appended labeling incorporating the Geriatric Use subsection.

/S/ Jan 4, 2000

Scheldon Kress, M.D. Date

cc:
NDA 19-810 SLR-062
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia /S/ 1-5-00
HFD-180/HGallo-Torres
HFD-180/SKress
HFD-181/MWalsh
HFD-180/AShaw
HFD-180/JChoudary
HFD-180/LZhou
f/t 1/5/00 jgw

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-810/S062

ADMINISTRATIVE DOCUMENTS

FEB 24 2000

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-810/SLR-062

Name of Drug: Prilosec (omeprazole) Delayed-Release Tablets

Sponsor: AstraZeneca LP

Material Reviewed

Submission Date(s): August 30, 1999

Receipt Date(s): August 31, 1999

Background and Summary Description: Supplement 062 provides for revision of the PRECAUTIONS section of the package insert to include a *Geriatric Use* subsection.

Review

The submitted draft labeling was compared to the currently approved labeling, identified as 9194131/64000431 and submitted in annual report 010 on November 12, 1999. The following difference was noted.

> A *Geriatric Use* subsection was added to the PRECAUTIONS section of the package insert as follows:
>
> "Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.
>
> Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See **CLINICAL PHARMACOLOGY**)."

The Medical Officer has accepted this revision in the review dated January 5, 2000 and has recommended approval of this supplement.

APPEARS THIS WAY
ON ORIGINAL

Conclusions

No differences other than the proposed *Geriatric Use* subsection were found between the currently approved labeling and the submitted draft labeling. Therefore, the supplement should be approved with the submitted draft labeling as recommended by the Medical Officer.

(S1) 2/23/00
Maria R. Walsh. M.S.
Regulatory Project Manager

(S1) 2-24-00

cc:
Original NDA 19-810/S-062
HFD-180/Div. Files .
HFD-180/M.Walsh

final: M.Walsh 2/23/00
filename: [redacted]

PM REVIEW

APPEARS THIS WAY
ON ORIGINAL