DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUL 18 2000

Mr. Douglas N. Dobak
Quality Liaison Leader
AstraZeneca L.P.
725 Chesterbrook Blvd.
Wayne, PA 19087

RE: NDA #19-810
Prilosec (omeprazole) Delayed-Release Capsules
MACMIS ID #9086

Dear Mr. Dobak:

This letter concerns AstraZeneca L.P.'s (AstraZeneca's) dissemination of promotional labeling and advertising for Prilosec (omeprazole) Delayed-Release Tablets. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed Prilosec promotional materials (sales aids #162159, #162105, #160452, reprint carrier #161856, and advertisement #0120PEOP), as part of its monitoring program and has concluded that AstraZeneca is disseminating materials that contain misleading promotional claims in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations. A description of our objections follows.

Misleading Efficacy Claims based on Intragastric pH Levels

Prilosec promotional materials use intragastric pH data from healthy volunteers to suggest that specific levels of intragastric pH acidity correlate with clinical efficacy in the treatment of erosive esophagitis (EE) patients. However, the relationship between specific intragastric pH levels in healthy volunteers and the clinical efficacy of Prilosec in EE patients has not been demonstrated. The use of nonclinical data to suggest a clinical benefit where none exists is misleading. Prilosec promotional materials also use intragastric pH level data to suggest that the clinical effect of Prilosec is superior to that of lansoprazole. The use of nonclinical data to suggest superiority to another drug is misleading.

For example, Sales Aid #160452 presents a graphical comparison of the lengths of time that Prilosec and lansoprazole each cause intragastric acidity levels in healthy volunteers to exceed a pH value > 4. The graph shows that 20 mg and 40 mg doses of Prilosec result in pH levels > 4 for 53% and 78% of the day respectively, while lansoprazole 30mg and 60 mg doses result in pH levels >4 for only 46% and 70% of the day respectively. The implication that, at both doses, Prilosec's clinical efficacy depends on its ability to maintain an intragastric pH level >4 for a certain percentage of time, is misleading. Similarly, the implication that the pattern and extent of Prilosec's daily intragastric acid suppression translates into an improved clinical benefit for Prilosec over lansoprazole in the EE patient, is misleading.

The small, bifurcated statement at the bottom of the page that "Intragastric pH levels are not indicative of efficacy of healing" is not sufficient to correct the overwhelming message that Prilosec's intragastric pH level correlates with clinical benefit. The tiny footnote that P=NS, is also not sufficient to correct the overall misleading message that Prilosec is superior to lansoprazole in clinical effect due to superior acid suppression in healthy volunteers.

Misleading Dose-Related Duration of Effect Claims

Prilosec's promotional materials misleadingly suggest that increasing the dose of Prilosec will result in an increased clinical efficacy in the treatment of erosive esophagitis or duodenal ulcers due to the increased duration of Prilosec's antisecretory effect at higher doses. For example, Sales Aid #160452 states that "*as you increase the dose of PRILOSEC, you can increase acid inhibition.*" An accompanying graph shows that the dose of Prilosec 40 mg suppresses acid (pH>3) for a duration of 22 hours a day while lower doses of Prilosec suppress acid for a shorter duration of time throughout the day. Although the Sales Aid is directed at the erosive esophagitis indication, the graph measures pH levels in duodenal ulcer patients. The graph and accompanying text in Sales Aid #160452, implies that both erosive esophagitis and duodenal ulcer patients will benefit from higher doses of Prilosec due to a correlation between increased clinical effect and increased duration of antisecretory effect.

There is, however, no substantial evidence to prove that a dose-related increase in duration of antisecretory action of Prilosec results in an increased clinical benefit in the treatment of EE or duodenal ulcers. In fact, the CLINICAL STUDIES section of the approved product labeling for Prilosec states that [for erosive esophagitis] "*the 40 mg dose was not superior to the 20 mg dose of Prilosec in the percentage healing rate.*" Similarly, the CLINICAL STUDIES section of the approved product labeling for Prilosec states that [for duodenal ulcers] "*At 2 and 4 weeks...40mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant difference...*" Thus, the suggestion of improved clinical effect, based on the Prilosec's duration of antisecretory effect in the promotional materials where no such effect has been demonstrated, is misleading.

Promotion of Unapproved Dosage Regimens

Prilosec promotional materials suggest dosage regimens for the treatment of erosive esophagitis and duodenal ulcers that are not supported by substantial evidence and are inconsistent with approved product labeling for Prilosec. Specifically, these materials promote a dose of 40 mg/day for both conditions for a duration of up to 12 years. Prilosec, however, is indicated for the short-term treatment of both conditions at an approved dose of 20mg/day for a period of 4 to 8 weeks.

- Erosive Esophagitis (EE) – The approved product labeling for Prilosec states that Prilosec is indicated for short-term therapy (4-8 weeks) of erosive esophagitis and that the efficacy of Prilosec used for longer than 8 weeks in EE patients has not been established. Prilosec's recommended adult oral dose for erosive esophagitis treatment is 20 mg daily. However, Sales Aid #162105 claims that "No PPI has been proven better in healing erosive esophagitis," that Prilosec has "excellent long-term safety data – up to 12 years of follow-up in patients receiving continuous treatment," and that "with Prilosec you can increase the dose to 40 mg without increasing adverse events." This Sales Aid is misleading because it suggests an unapproved dosage regimen for EE. The Sales Aid presents the results of 12-year follow-up safety studies involving Prilosec, implying that Prilosec is safe and effective in the long-term or chronic treatment of erosive esophagitis.

- Duodenal Ulcer Indication - Similarly, the approved dose of Prilosec in the short-term treatment of duodenal ulcer is 20 mg per day for a period of four weeks for most patients. Sales Aid #160452 suggests that a 40 mg/day dose of Prilosec is superior to a 20 mg/day dose in the treatment of duodenal ulcers and that a period of continuous therapeutic use up to eleven years is appropriate. The Sales Aid is misleading because its claims are inconsistent with the approved product labeling for Prilosec. The tiny footnote in the Sales Aid stating that the 20 mg dose is indicated for active duodenal ulcer is inadequate to correct the overwhelming message of the large and colorful graph that suggests an increased clinical effect from the 40 mg dose for duodenal ulcer patients, and the text that suggests long-term continuous treatment is appropriate.

Misleading Comparative Presentations of EE Healing Rates

Reprint Carrier #161856 makes misleading graphical and textual comparisons between the EE healing rates of Prilosec and other Proton Pump Inhibitors (PPIs), based on the Castell study. The upper graph in Reprint Carrier #161856 is entitled "Healing Rates in Patients with Erosive Esophagitis." The graph is misleading because it does not prominently disclose the placebo effect from the Castell Study at 4 and 8 weeks, nor does

it prominently disclose the lack of statistical significance of some of the numbers shown.

The accompanying statement that "No PPI is proven to work better...for healing all grades of erosive esophagitis in clinical trials" is also not accurate, since the Castell study (and other cited references) did not make head-to-head comparisons between the healing rates of Prilosec and all other PPIs, delineated by each grade of erosion severity. In addition, the reprint carrier presents healing rates for EE that are inconsistent with the approved product labeling.

Misrepresentative Healing Rates in Severe EE

Sales Aid #162159 compares a combined EE healing rate of 89% for Prilosec 20 mg in patients with grades 3 and 4 erosive esophagitis, to a combined EE healing rate of 85% for lansoprazole 30 mg. The accompanying text states: "No PPI is proven to work better...in severe erosive esophagitis in clinical trials." The graph, however, misrepresents the extent of Prilosec experience in severe EE patients because it does not present the background incidence rate of patients studied that had the most severe erosions of grade 4. In the actual study, less than 7% of the Prilosec patients (and less than 9% of the lansoprazole patients) had an erosion severity of grade 4, and less than 27% of the Prilosec (and approximately 30% of the lansoprazole patients) had an EE erosion severity rate of grade 3. Thus, the healing rate of 89% for Prilosec and its comparison to healing rate of 85% for lansoprazole, for erosion severity of grades 3 and 4, without additional background incidence, suggests that the drug has been studied in a larger population of grade 4 erosion patients than it actually has been studied. The Sales Aid misrepresents the extent of experience with this drug in healing erosions in grade 4 patients.

Misleading Presentation of Clinical Data re Heartburn Relief

Reprint Carrier #161856, (Castell et al), selectively presents data from the Castell study. The front flap of the reprint carrier states that "Prilosec 20mg and lansoprazole 30mg provided comparable decreases in heartburn in patients with EE. There were only minor and inconsistent differences in heartburn symptom assessments." However, on page 1753 of the actual reprint, the article states, "Patient diaries revealed significant differences between active treatment groups in the relief of day and night heartburn (Table 2). Patients receiving lansoprazole 30 mg reported significantly less day and night heartburn during the first day and the first week of treatment than did patients receiving omeprazole 20mg (Table 2). Similar results were observed when diary entries from the intent-to-treat population were evaluated." The Castell reprint summary also stated that lansoprazole provided superior symptomatic relief early in the treatment and was more effective than omeprazole 20 mg with respect to alleviating nighttime heartburn throughout the 8-wk course of therapy. Thus, the claims of comparable heartburn relief between omeprazole and lansoprazole are not supported by the referenced study.

Expanded Indication

Advertisement #0120PEOP promotes Prilosec for the relief of heartburn without adequately describing Prilosec's approved indication. Prilosec is indicated for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD). Heartburn related to GERD or acid reflux disease is heartburn that occurs two (2) or more days a week and persists despite diet or treatment. Prilosec is not indicated for the occasional relief of heartburn in the absence of GERD.

Lack of Fair Balance

The promotional materials are lacking in fair balance because the risk information is not presented in a manner that is reasonably comparable to the presentation of promotional claims for PRILOSEC. Promotional materials must present information relating to contraindications, warnings, precautions and adverse effects with a prominence and readability reasonably comparable with the presentation of information relating to the efficacy of the drug.

For example, Sales Aid #162105 states, in large-size colorful header font, that Prilosec has an "Excellent safety record...ZERO cases of ECL cell dysplasia or carcinoids in continuous, open label studies of up to 12 years...With PRILOSEC you can increase the dose to 40mg without increasing adverse events." In much smaller type at the bottom of the page, however, the balancing statements that "Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors...PRILOSEC should be used only for the conditions, dosage, and duration specified in the Prescribing Information." This important safety information is not presented with reasonably comparable readability to the efficacy claims presented and lacks fair balance.

In addition, some of the Prilosec materials lack important risk information. Sales Aid #162159, for example, states a Prilosec claim for the indication of H. pylori-associated duodenal ulcer disease in combination with clarithromycin and amoxicillin. The Sales Aid, however, fails to include any important risk information that accompanies the use of Prilosec in combination with clarithromycin and amoxicillin. Specifically, the approved product labeling for Prilosec states that clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics, that clarithromycin is contraindicated in patients receiving cisapride, or pimozide who have pre-existing cardiac abnormalities or electrolyte disturbances, and that clarithromycin should not be used in pregnant women except in circumstances where no alternative therapy is appropriate. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. The Prilosec labeling also states that amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins.

Reprint Carrier #161856 also fails to provide fair balance. The carrier extensively details the efficacy results of the Castell study on each page, while limiting the safety information related to the study to one statement detailing the three most common adverse events of the study: headache, and diarrhea and abdominal pain. However, in the study, nausea was also a common adverse event, that was not mentioned in the carrier, nor does the carrier mention the severe adverse reactions to omeprazole 20 mg that were experienced by the patients in the study. In the Castell study, four omeprazole 20 mg patients developed severe events that were possibly or probably treatment–related, including rhabdomyolysis, uticarial wheals, severe headache, and severe thromobocytopenic fever.

Requested Action

In order to address these objections, DDMAC requests that AstraZeneca:

1. Immediately ceases further use of these and other materials and practices with the same or similar messages.

2. Provide DDMAC, in writing, with AstraZeneca's intent to comply with the above. This response should include a list of all violative promotional materials and AstraZeneca's methods for discontinuing their use.

AstraZeneca's response should be received no later than July 28, 2000. If you have any questions, you should direct them to the undersigned in writing or by facsimile at (301) 594-6759 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds AstraZeneca that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9086 in addition to the NDA number.

Sincerely,

/S/

Patricia Kuker Staub, R.Ph, J.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Only PRILOSEC offers all of these benefits:

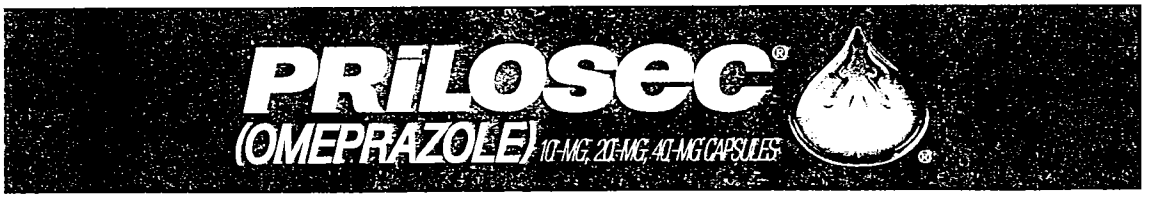
EFFICACY ... ***complete*** **relief of symptoms**

24-hour complete relief of heartburn in 84% of GERD patients in controlled studies[1]*

SAFETY ... **more than a decade of long-term safety data**

Excellent safety profile in ongoing studies of patients treated continuously for up to 11 years[2]

CONFIDENCE ... **America's most prescribed anti-secretory, surpassing any H_2-RA or PPI**[3]*



The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain.

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

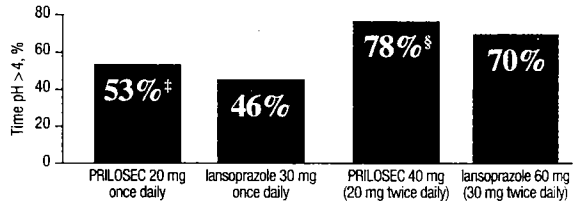
Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long term with omeprazole.

*In 6 studies involving patients with erosive esophagitis.
†IMS HEALTH, since May 1997.

Before prescribing PRILOSEC, please see accompanying full Prescribing Information.

PRILOSEC provides excellent acid suppression

Percentage of time intragastric pH maintained above 4 over 24 hours[4]



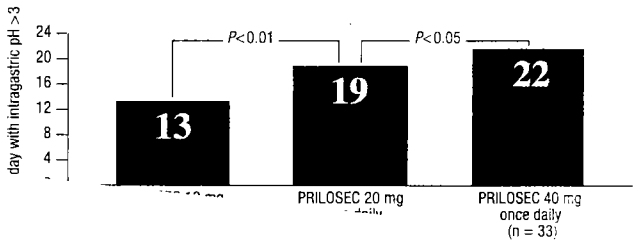
‡ P = NS vs lansoprazole 30 mg.
§ P = 0.0309 vs lansoprazole 60 mg.
Data from a 1-week, randomized, single-blind, 4-way crossover study in healthy *H pylori*-negative patients (n = 16).

Adapted from Geus, et al[4]

- PRILOSEC 20 mg once daily is appropriate for the majority of acid sufferers[1]
- PRILOSEC 40 mg once daily is appropriate for conditions that require greater acid control[2]

As you increase the dose of PRILOSEC, you can increase acid inhibition

Mean duration of antisecretory effect with various doses of PRILOSEC[5]



Adapted from Savarino, et al[5]

Intragastric

The most fi

PRILOSEC

[1] Indicated for h
esophagitis, m
[2] Indicated for t
Helicobacter
[3] Registered tr
PRILOSEC s
Before prescr

References:
Acid-inhibit
5. Savarino V, Mela GS. [illegible]

Please visit our web site at www.prilosec-us.com

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PRILOSEC (OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

Anzemet dolasetron mesylate

[illegible] in the Prescribing Information.
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PR119. 3. Data on file. DA-PRI[illegible]. 4. Geus WP, Mulder PGH, Nicolai JJ, et al. *ri*-negative healthy subjects. *Aliment Pharmacol Ther.* 1995;9:329-335.
o various doses of omeprazole. *Dig Dis Sci.* 1994;39:161-168.

AstraZeneca

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160452

Printed in U.S.A.

PRiLOSEC®

(OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

Extensive clinical experience

- **The PPI innovator with more than 18 years of clinical experience worldwide[1]**
- **Over 345 million patient treatments* worldwide[2†]**

Excellent long-term safety data

- **Up to 12 years of follow-up in patients receiving continuous treatment[3]**

Proven efficacy

- **No PPI is proven more effective in healing erosive esophagitis[4-11]**

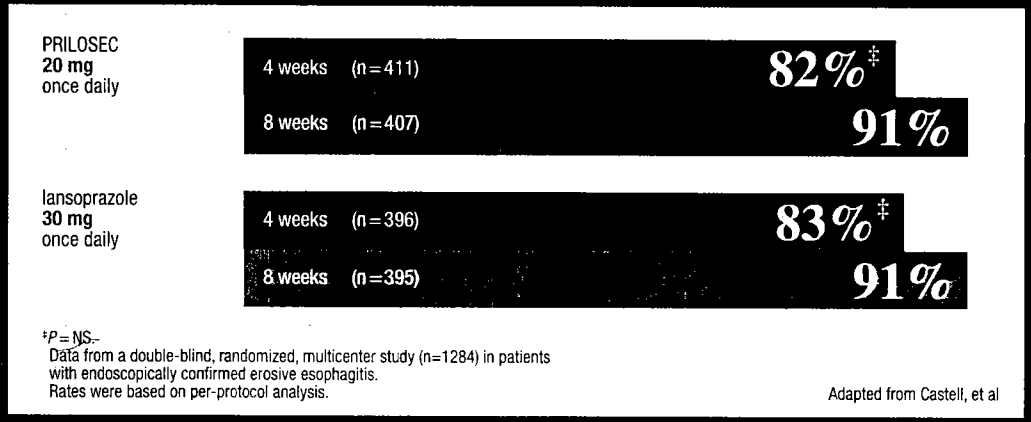
The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long term with omeprazole.

PRILOSEC is indicated first line for heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), erosive esophagitis, maintenance of healed erosive esophagitis, active duodenal ulcer, active benign gastric ulcer, pathological hypersecretory conditions, and in combination with clarithromycin and amoxicillin or with clarithromycin for *Helicobacter pylori*-associated duodenal ulcer disease.

Before prescribing PRILOSEC, please see accompanying full Prescribing Information.

NO PPI is proven to work better...
for healing all grades of erosive esophagitis in clinical trials[4-11]

Healing rates in patients with erosive esophagitis[4]

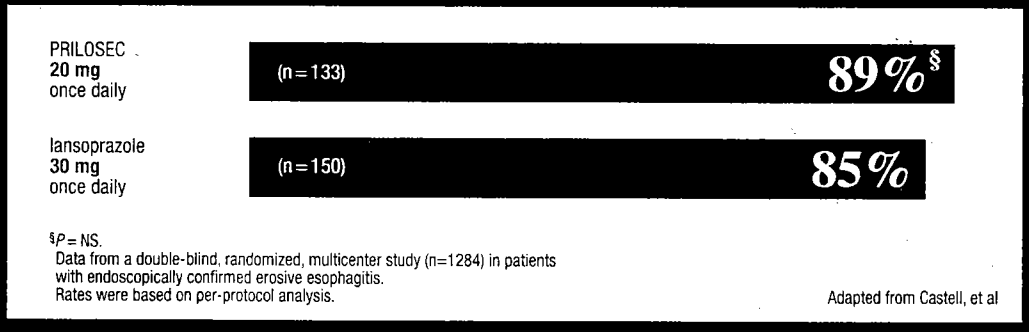


‡*P* = NS.
Data from a double-blind, randomized, multicenter study (n=1284) in patients with endoscopically confirmed erosive esophagitis.
Rates were based on per-protocol analysis.

Adapted from Castell, et al

in severe erosive esophagitis in clinical trials[4,5,7]

8-Week healing rates for patients with baseline esophagitis (grades 3 and 4)[4]



§*P* = NS.
Data from a double-blind, randomized, multicenter study (n=1284) in patients with endoscopically confirmed erosive esophagitis.
Rates were based on per-protocol analysis.

Adapted from Castell, et al

The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain.

*A patient treatment is defined as an individual prescription calculated by IMS to be an average of 41.31 counting units.
†IMS MIDAS Database 1/89 - 6/99
¶Registered trademarks of the AstraZeneca group of companies.

PRILOSEC should be used only for the conditions, dosage, and duration specified in the Prescribing Information.

Before prescribing PRILOSEC, please see accompanying full Prescribing Information.

References: 1. Data on file, DA-PRI33. **2.** Data on file, DA-PRI34. **3.** Data on file, DA-PRI31. **4.** Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. *Am J Gastroenterol.* 1996;91(9):1749-1757. **5.** Mee AS, Rowley JL, the Lansoprazole Clinical Research Group. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Aliment Pharmacol Ther.* 1996;10:757-763. **6.** Hatlebakk JG, Berstad A, Carling L, et al. Lansoprazole versus omeprazole in short-term treatment of reflux oesophagitis: results of a Scandinavian multicentre trial. *Scand J Gastroenterol.* 1993;28:224-228. **7.** Dekkers CPM, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 1999;13:49-57. **8.** Delchier JC, Cohen G, Humphries TJ. Rabeprazole is comparable in efficacy to omeprazole in erosive GORD and provides more rapid heartburn relief. *Gut.* 1994;44(suppl 1):A112. **9.** Corinaldesi R, Valentini M, Belaiche J, et al. Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. *Aliment Pharmacol Ther.* 1995;9:667-671. **10.** Mössner J, Hölscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther.* 1995;9:321-326. **11.** Vicari F, Belin J, Marek L. Pantoprazole 40 mg versus omeprazole 20 mg in the treatment of reflux oesophagitis: results of a French multicentric double-blind comparative trial. *Digestion.* 1998;59(suppl 3):608.

PRiLOSEC®¶
(OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

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It's time for a Prilosec summer.

Spread the word with a FREE phone card.

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You already know that the makers of prescription PRILOSEC are the experts in acid reflux disease. And that PRILOSEC can help keep you heartburn free. Now you can tell your friends who may suffer from frequent and persistent heartburn about PRILOSEC. Just call today for your free 24-minute phone card. And remember to take your PRILOSEC as directed for 24 hours of complete heartburn relief that's possible with PRILOSEC. The most common side effects are headache, diarrhea, and abdominal pain.*

*Offer expires 9/30/00. Limit one per household. Please allow 4 to 6 weeks for delivery.

AstraZeneca

Please read the important Product Information on the following page and discuss it with your doctor.

PRILOSEC®† (OMEPRAZOLE) 20 mg CAPSULES

Please read this summary carefully, and then ask your doctor about PRILOSEC. No advertisement can provide all the information needed to prescribe a drug. This advertisement does not take the place of careful discussions with your doctor. *Only your doctor* has the training to weigh the risks and benefits of a prescription drug for you.

PRILOSEC® (OMEPRAZOLE) Delayed-Release Capsules*

BRIEF SUMMARY.

CLINICAL PHARMACOLOGY ***Pharmacokinetics and Metabolism: Omeprazole*** – 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.

INDICATIONS AND USAGE ***Duodenal Ulcer:*** PRILOSEC is indicated for short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy. PRILOSEC, in combination with clarithromycin and amoxicillin, is 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, in combination with clarithromycin, is also 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. 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 the clarithromycin package insert, MICROBIOLOGY section.) ***Gastric Ulcer:*** PRILOSEC is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. ***Treatment of Gastroesophageal Reflux Disease (GERD):*** **Symptomatic GERD** – PRILOSEC is indicated for the treatment of heartburn and other symptoms associated with GERD. **Erosive Esophagitis** – PRILOSEC is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. 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 is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months. ***Pathological Hypersecretory Conditions:*** PRILOSEC is indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS ***Omeprazole:*** PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation. ***Clarithromycin:*** Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic. Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.) ***Amoxicillin:*** Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

WARNINGS: ***Clarithromycin:*** **CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)** ***Amoxicillin:*** SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.** (See WARNINGS in prescribing information for amoxicillin.) ***Antimicrobials:*** **Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** (see WARNINGS in prescribing information for clarithromycin and amoxicillin.)

PRECAUTIONS ***General:*** Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole. ***Information for Patients:*** PRILOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole. ***Drug Interactions:*** Other – Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC. Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of PRILOSEC. **Combination Therapy with Clarithromycin** – Co-administration of omeprazole and clarithromycin have resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics: Combination Therapy with Antimicrobials* in full Prescribing Information.) 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.) ***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/kg/day omeprazole (approximately 35 times the human dose) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. 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 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. 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 825 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. ***Pregnancy:*** **Omeprazole: Pregnancy Category C** – In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Clarithromycin: Pregnancy Category C** – See WARNING (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 discontinue the drug, taking into account the importance of the drug to the mother. ***Pediatric Use:*** Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: 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* (omeprazole). 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. *Combination Therapy for H. pylori Eradication:* dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin, and amoxicillin. 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. *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 or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.

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.

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 4 weeks. Some patients may require an additional 4 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 to 8 weeks. (See 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. ***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. No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.

Distributed by: Astra Pharmaceuticals, L.P.
Wayne, PA 19087, USA

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

December 1998

PRI31

NOTE: This summary provides important information about PRILOSEC. If you would like more information, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them.

*Registered trademark of Astra AB.

PRiLOSEC®

(OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

Extensive clinical experience

- **The PPI innovator with more than 18 years of clinical experience worldwide[1]**
- **Over 345 million patient treatments* worldwide[2†]**

Excellent long-term safety data

- **Up to 12 years of follow-up in patients receiving continuous treatment[3]**

Proven efficacy

- **No PPI is proven more effective in healing erosive esophagitis[4-11]**

The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain. Symptomatic response to therapy 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.

*A patient treatment is defined as an individual prescription calculated by IMS to be an average of 41.31 counting units.
†IMS MIDAS Database 1/89 - 6/99.

PRILOSEC is indicated first line for heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), erosive esophagitis, maintenance of healed erosive esophagitis, active duodenal ulcer, active benign gastric ulcer, pathological hypersecretory conditions, and in combination with clarithromycin and amoxicillin or with clarithromycin for *Helicobacter pylori*-associated duodenal ulcer disease.

Before prescribing PRILOSEC, please see accompanying full Prescribing Information.

Excellent safety record

PRILOSEC has the longest ongoing clinical study of any PPI—up to 12 years[3]

ZERO

cases of ECL cell dysplasia or carcinoids in continuous, open-label studies of up to 12 years[3‡§]

With PRILOSEC you can increase the dose to 40 mg without increasing adverse events[12,13¶]

- **No dose-related diarrhea observed with PRILOSEC 20-mg or 40-mg capsules[12,13]**

Adverse events profile of PRILOSEC is comparable to placebo[12-14]

The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long term with omeprazole.

‡Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

§Patients were refractory to treatment with H_2-RAs for either peptic ulcer disease or GERD and received omeprazole 20 mg to 40 mg daily. Follow-up included upper endoscopy with gastric biopsy for mucosal pathology assessment of gastric ECL cells at 12-month intervals and clinical history evaluations at 6-month intervals.

¶PRILOSEC should be used only for the conditions, dosage, and duration specified in the Prescribing Information.

**Registered trademarks of the AstraZeneca group of companies.

References: 1. Data on file, DA-PRI33. **2.** Data on file, DA-PRI34. **3.** Data on file, DA-PRI31. **4.** Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. *Am J Gastroenterol.* 1996;91(9):1749-1757. **5.** Mee AS, Rowley JL, the Lansoprazole Clinical Research Group. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Aliment Pharmacol Ther.* 1996;10:757-763. **6.** Hatlebakk JG, Berstad A, Carling L, et al. Lansoprazole versus omeprazole in short-term treatment of reflux oesophagitis: results of a Scandinavian multicentre trial. *Scand J Gastroenterol.* 1993;28:224-228. **7.** Dekkers CPM, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 1999;13:49-57. **8.** Delchier JC, Cohen G, Humphries TJ. Rabeprazole is comparable in efficacy to omeprazole in erosive GORD and provides more rapid heartburn relief. *Gut.* 1994;44(suppl 1):A112. **9.** Corinaldesi R, Valentini M, Belaïche J, et al. Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. *Aliment Pharmacol Ther.* 1995;9:667-671. **10.** Mössner J, Hölscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther.* 1995;9:321-326. **11.** Vicari F, Belin J, Marek L. Pantoprazole 40 mg versus omeprazole 20 mg in the treatment of reflux oesophagitis: results of a French multicentric double-blind comparative trial. *Digestion.* 1998;59(suppl 3):608. **12.** Simon TJ, Bradstreet DC. Comparative tolerability profile of omeprazole in clinical trials. *Dig Dis Sci.* 1991;36(10):1384-1389. **13.** Valenzuela JE, Kogut DG, McCullough AJ, et al. Comparison of once-daily doses of omeprazole (40 and 20 mg) and placebo in the treatment of benign gastric ulcer: a multicenter, randomized, double-blind study. *Am J Gastroenterol.* 1996;91(12):2516-2522. **14.** Prescribing Information for PRILOSEC.

Before prescribing PRILOSEC, please see accompanying full Prescribing Information.

PRILOSEC® (OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

AstraZeneca

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A Comparative Study Demonstrating the Efficacy of Omeprazole and Lansoprazole in Healing Erosive Esophagitis (EE)

Efficacy and Safety of Lansoprazole in the Treatment of Erosive Reflux Esophagitis

Castell DO,
Richter JE,
Robinson M, et al.
Am J Gastroenterol. 1996;91(9):1749-1757.

This study was supported by TAP Pharmaceuticals.

Castell et al

METHODS

- In this double-blind, multicenter study, 1284 patients with endoscopically confirmed erosive reflux esophagitis were randomized to receive omeprazole 20 mg (n = 431), lansoprazole 30 mg (n = 422), lansoprazole 15 mg (n = 218),* or placebo (n = 213) once daily for 8 weeks. Healing was evaluated endoscopically at 2-week intervals. Patients kept daily diaries of their symptoms.

RESULTS—*Heartburn Symptom Reduction*

- PRILOSEC 20 mg and lansoprazole 30 mg provided comparable decreases in heartburn in patients with EE[1].

- There were only minor and inconsistent differences in heartburn symptom assessments[1].

	Investigator Assessment	Patient Diary Assessment	
	Day and Night heartburn	Days with heartburn	Nights with heartburn
Week 1 (7-day period)	No significant difference	0.3 fewer with lansoprazole	0.4 fewer with lansoprazole
Week 8 (56-day period)	No significant difference	No significant difference	1.3 fewer with lansoprazole

Adapted from Castell, et al[1]

The clinical relevance of these minor differences is unclear.

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

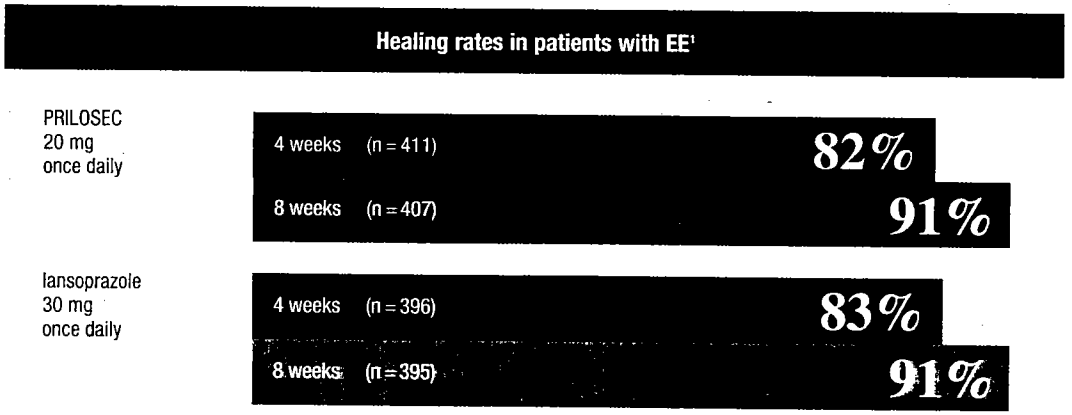
PRILOSEC should be used only for the conditions, dosage, and duration specified in the Prescribing Information.

*Note: This study contains information on the use of lansoprazole 15 mg once daily for the treatment of erosive esophagitis, a dose that is not approved in the product labeling for Prevacid® (lansoprazole). The current recommended adult oral dose of lansoprazole for the treatment of erosive esophagitis is 30 mg once daily. Statements in this publication that lansoprazole dose is superior to omeprazole dose in providing symptomatic relief in erosive esophagitis patients are not approved in the product labeling for Prevacid®.

Castell et al

RESULTS—*Healing*

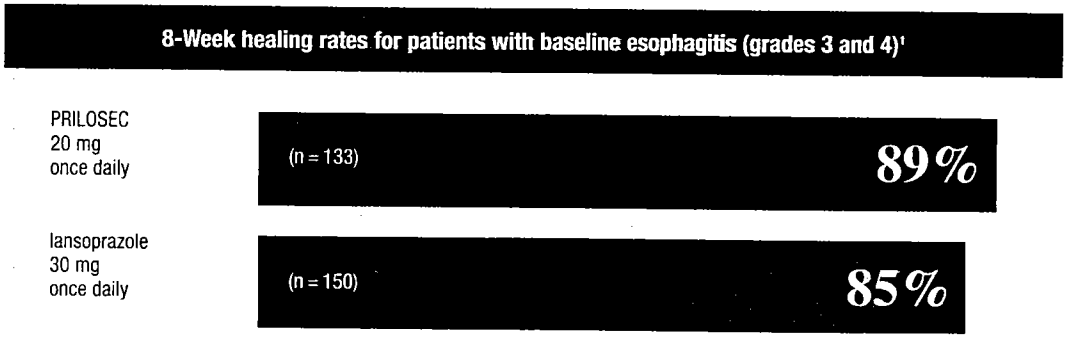
PRILOSEC achieved excellent healing rates in patients with EE[1].



Rates were based on per-protocol analysis.

Adapted from Castell, et al[1]

PRILOSEC achieved excellent healing rates in patients with more severe EE[1].



Rates were based on per-protocol analysis.

Adapted from Castell, et al[1]

The most frequently reported adverse events with PRILOSEC are headache, diarrhea, and abdominal pain.

Please see accompanying full Prescribing Information.

PRiLOSeC®
(OMEPRAZOLE) 20 MG ONCE DAILY

PRILOSEC®*
(OMEPRAZOLE) 10-MG, 20-MG, 40-MG CAPSULES

*PRILOSEC is a registered trademark of the AstraZeneca group of companies.

Please visit our web site at www.prilosec-us.com

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