

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-810/S-008

Trade Name: Prilosec

Generic Name: Omeprazole

Sponsor: Merck Research Laboratories

Approval Date: January 27, 1992

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APPLICATION NUMBER:

NDA 19-810/S-008

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APPROVAL LETTER

Food and Drug Administration
Rockville MD 20857

NDA 19-810/S-008

Merck Sharp & Dohme Research Laboratories
Attention: James T. Molt, Ph.D.
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

Dear Dr. Molt:

Please refer to your January 17, 1991, supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Capsules, 20 mg.

We also acknowledge receipt of your amendments dated July 1, July 3, September 5, and December 13, 1991.

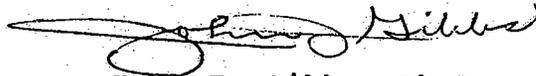
We also acknowledge receipt of your letter dated January 17, 1992, notifying us of your commitment to provide responses after approval to the questions raised in our letter dated January 7, 1992.

The supplemental application provides for a change in manufacturing site to West Point, Pennsylvania and Kirkland, Canada.

We have completed the review of this supplemental application and it is approved.

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

Sincerely yours,



John J. Gibbs, Ph.D.
Supervisory Chemist
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

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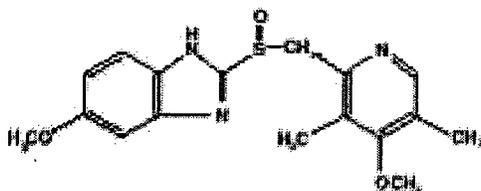
APPROVED LABELING

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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 C₁₇H₁₉N₃O₃S, with a molecular weight of 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.

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 m², 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.

PRILOSEC Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, PRILOSEC Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for PRILOSEC Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

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 increases 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 C_{max} 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 Dose¹

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. Intra-gastric 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 H₂-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 H₂-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		Ranitidine
	20 mg (n = 34)	40 mg (n = 36)	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 + clarithromycin + 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, multicenter 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] ^{†*} (n = 53)	0 [0, 7] (n = 54)	31 [18, 47] (n = 42)
Study M93-100	64 [51, 76] ^{†*} (n = 61)	0 [0, 6] (n = 59)	39 [24, 55] (n = 44)
Non U.S. Studies			
Study M92-812b	83 [71, 92] [†] (n = 60)	1 [0, 7] (n = 74)	N/A
Study M93-058	74 [64, 83] [†] (n = 86)	1 [0, 6] (n = 90)	N/A

[†] Statistically significantly higher than clarithromycin monotherapy (p < 0.05)

* 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 <i>H. pylori</i> Eradication Status % of Patients with Ulcer Recurrence		
	<i>H. pylori</i> eradicated*	<i>H. pylori</i> not eradicated*
U.S. Studies †		
6 months post-treatment		
Study M93-067	35 (n = 49)	60 (n = 88)
Study M93-100	8 (n = 53)	60 (n = 106)
Non U.S. Studies ‡		
6 months post-treatment		
Study M92-812b	5 (n = 43)	46 (n = 78)
Study M93-058	6 (n = 53)	43 (n = 107)
12 months post-treatment		
Study M92-812b	5 (n = 39)	68 (n = 71)

* *H. pylori* eradication status assessed at same timepoint as ulcer recurrence

† Combined results for PRILOSEC + clarithromycin, PRILOSEC, and clarithromycin treatment arms

‡ Combined results for PRILOSEC + clarithromycin and PRILOSEC treatment arms

* (p < 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 H₂-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 H₂-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 $\mu\text{g/mL}$) 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ by Etest[®].

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes*					
Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results			
		<i>H. pylori</i> negative - eradicated	<i>H. pylori</i> positive - not eradicated		
		Post-treatment susceptibility results			
		S ^b	I ^b	R ^b	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 ^b	108	72	1	26	9
Intermediate ^b	1			1	
Resistant ^b	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 ^b	171	153	7	3	8
Intermediate ^b					
Resistant ^b	14	4	1	6	3

*Includes only patients with pretreatment clarithromycin susceptibility test results

^bSusceptible (S) MIC ≤ 0.25 µg/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 MICs¹. 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 ($\mu\text{g/mL}$) ^a	Interpretation
≤ 0.25	Susceptible (S)
0.5 - 1.0	Intermediate (I)
≥ 2.0	Resistant (R)

Amoxicillin MIC ($\mu\text{g/mL}$) ^{a,b}	Interpretation
≤ 0.25	Susceptible (S)

^a These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

^b There were not enough organisms with MICs > 0.25 $\mu\text{g/mL}$ 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 ($\mu\text{g/mL}$) ^a
<i>H. pylori</i> ATCC 43504	Clarithromycin	0.015 - 0.12 ($\mu\text{g/mL}$)
<i>H. pylori</i> ATCC 43504	Amoxicillin	0.015 - 0.12 ($\mu\text{g/mL}$)

^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, pimozone, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozone, 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.

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

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 pregnancy. 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 \geq 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
<i>Body as a Whole, site unspecified</i>		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
<i>Digestive System</i>		
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
<i>Nervous System/Psychiatric</i>		
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.

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

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).

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Manufactured for: AstraZeneca LP, Wilmington, DE 19850

By: Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

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AstraZeneca 

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-810/S-008

APPROVABLE LETTER

copy 431

JAN - 7 1992

NDA 19-810/S-008

Merck Sharp and Dohme
Attention: James T. Molt, Ph.D.
West Point, Pennsylvania 19486

Dear Dr. Molt:

Please refer to your January 17, 1991 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Capsules, 20 mg.

We also acknowledge receipt of your amendments dated July 1, July 3, September 5, and December 13, 1991.

The supplemental application provides for a change in manufacturing site to West Point, Pennsylvania and Kirkland, Canada.

We have completed the review of this supplemental application as amended. Before this supplement may be approved, however, satisfactory cGMP inspection for both facilities must be obtained. We also request that you provide responses to the following questions. Such responses may be provided now or after approval.

1. Provide limits on the amount of / _____ material in each batch.
2. Provide the data allowing the calculation of the yield specifications after / _____ / they become available.
3. Place specific references to the / _____ and SOP in the manufacturing batch record for the / _____.
4. Provide all of the data from the in-process tests.
5. Convert the / _____ in the future when a sufficient data base has been accumulated.
6. In the discussion of the _____ for the enteric-coated particles _____ provide the following information:
 - a. A copy of the spectrum from an untreated sample.
 - b. Data showing that the measurement of / _____ / _____ nm is linear with concentration over the expected range of concentrations.

- c. Include a step / _____ /
7. The validation report for the effect of equilibration time on the assay of / _____ / at / _____ /, $\mu\text{g/ml}$ from Astra shows that the peak area declines at a rate of / _____ / per / _____ /, which can be significant after / _____ / hours. Perform the validation using your own equipment and demonstrate that there is no effect of equilibration time on the assay, particularly at the low concentrations expected for the test samples.
 8. Reply to our request that the / _____ / be made a release specification for the drug product, rather than an in-process control.
 9. Amend the printed manufacturing procedure to reflect the conditions actually being used / _____ / . Your operators should deviate from the printed procedure only with reasonable justification.
 10. Submit stability data for three lots manufactured under the current procedure before an expiration date based on / _____ / of existing data can be calculated.

In addition, please be aware of the fact that stability data in the original submission (Page 3A00243) shows that Astra-manufactured material was stable at / _____ / . While we recognize that this may be considered a stress condition, the fact that the Astra-manufactured material was stable under these conditions while the Merck-manufactured material is not is a sign that there is something different about the Merck-manufactured product. Therefore we will need to see more data before granting an expiration date based upon relatively short-term data at / _____ / . This is particularly important because the dissolution specifications for the drug product are not stringent. You may wish to consider a shorter expiration date / _____ / for Merck manufactured drug product.

11. Specify the container\closure and the temperature on the stability report.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw this application.

NDA 19-810/SCM-008
PAGE 3

Should you have any questions, please contact:

Thomas Hassall
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 19-810

HFD-180

HFD-181/CSO

HFD-180/SFredd

HFD-80/DDIR

HFD-180/AShaw/December 20, 1991

AS/dob/f/t 1-2-92/Wp # 19810112.1AS

2nd DRAFT 1-6-92/3rd draft 1-7-92

f/t 1-7-92

APPROVABLE

ABS 1/7/92
CP 1/7/92
[Signature] 1/7/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-810/S-008

NOT APPROVABLE LETTER

MAY 29 1991

Merck Sharp and Dohme
Attention: James T. Molt, Ph.D.
West Point, Pennsylvania 19486

Dear Dr. Molt:

Please refer to your January 17, 1991 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Capsules, 20 mg.

The supplemental application provides for a change in manufacturing site to West Point, Pennsylvania and Kirkland, Canada.

We have completed our review and find the information presented is inadequate and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). We note that you have not complied with specific requests as specified at our meeting of November 20, 1989. These are included in the following list. The deficiencies may be summarized as follows:

Regarding the Inactive Ingredients:

1. Please provide a description and specifications for the gelatin capsules.
2. Please provide the method used to measure the specific gravity of the SD3-A alcohol and explain why the value _____ is different from that listed for SD3-A alcohol in 27 CFR 21.161 (0.8149).
1. Please use an identification test for / — / which is less subjective than detection of the / _____ / or provided by the supplier on a certificate of analysis.

Regarding the manufacturing procedure:

1. In Section C, Validation Protocol you have listed the tests which will be done for three Manufacturing Formulas in order to demonstrate the reproducibility of the process. However the actual Manufacturing Procedure and Batch Records must include these tests, particularly for acceptance of each _____

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-
May 29, 1991
Cornespe

Should you have any questions, please contact:

Steven Budabin
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

John J. Gibbs, Ph. D.
Supervisory Chemist
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 19-810

HFD-180

HFD-181/CSO

HFD-180/SFredd

HFD-80/DDIR

HFD-180/JGibbs

HFD-180/AShaw/5/23/91

AShaw/dob/5-23-91/wp#198105.1AS

AS/dob/5-24-91/w5070e

SKS 5/25/91

ABS 5/28/91

SP 5/28/91

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-810/S-008

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1		1. Organization: HFD-180	2. NDA Number: 19-810
3. Name and Address of Applicant (City & State): Merck Sharp and Dohme West Point, PA 19486		4. AF Number:	
6. Name of Drug: Prilosec		7. Nonproprietary Name: Omeprazole MAY 24 1991	5. Supplement
		Numbers	Dates
		SCM-008	Jan 17, 1991
8. Supplement Provides for: changing the manufacturing site from Sweden to West Point, PA and Kirkland, Canada		9. Amendments and Other (Reports, etc.) Dates:	
10. Pharmacological Category: Anti-ulcer	11. How Dispensed: RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. Related IND/NDA/DMF(s):	
13. Dosage Form: Delayed-release capsule	14. Potency: 20 mg		
15. Chemical Name and Structure: 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole		16. Records and Reports:	
		Current <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
		Reviewed <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
17. Comments: The applicant has not responded adequately to our requests in the meeting held on Nov 19, 1990. See Review Notes ; cc: NDA 19-810 HFD-180/Div File HFD-181/CSO HFD-180/SFredd <input type="checkbox"/> HFD-180/AShaw R/D init by: JSieczkowski/for JGibbs/5/23/91 typist: AS/dob/5-23-91/f/t 5-24-91 Wp:19810105.OAS			
18. Conclusions and Recommendations: Not approvable			
19. Reviewer			
Name: Arthur B. Shaw, Ph.D.	Signature <i>Arthur B. Shaw</i>	Date Completed: 5/24/91	
Distribution / /Original Jacket / /Reviewer / /Division File			

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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CHEMIST'S REVIEW #1		1. Organization: HFD-180	2. NDA Number: 19-810
3. Name and Address of Applicant (City & State): Merck Sharp and Dohme West Point, PA 19486		NOV 12 1991	4. AF Number:
6. Name of Drug: Prilosec		7. Nonproprietary Name: Omeprazole	5. Supplement Numbers SCM-008 Dates Jan 17, 1991
8. Supplement Provides for: changing the manufacturing site from Sweden to West Point, PA and Kirkland, Canada		9. Amendments and Other (Reports, etc.) Dates: AC July 1, 1991	
10. Pharmacological Category: Anti-ulcer	11. How Dispensed: RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. Related IND/NDA/DMF(s):	
13. Dosage Form: Delayed-release capsule	14. Potency: 20 mg		
15. Chemical Name and Structure: 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole		16. Records and Reports: Current <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
17. Comments: The applicant has responded to the Agency's deficiency letter of May 29, 1991. See Review Notes cc: NDA 19-810 HFD-180/Div File HFD-181/CSO HFD-180/SFredd HFD-180/AShaw R/D init by: JGibbs/11-8-91 typist: AS/dob/11-8-91/FT Wp:19810111.0AS			
18. Conclusions and Recommendations: The sponsor should be asked to provide the requested information before any further review can be done.			
19. Reviewer			
Name: Arthur B. Shaw, Ph.D.	Signature <i>Arthur B. Shaw</i> 11/8/91	Date Completed: November 8, 1991	
Distribution / /Original Jacket / /Reviewer / /Division File			

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 § 552(b)(5) Deliberative Process

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CHEMIST'S REVIEW #3		1. <u>Organization:</u> HFD-180	2. <u>NDA Number:</u> 19-810
3. <u>Name and Address of Applicant (City & State):</u> Merck Sharp and Dohme West Point, PA 19486 Address		4. <u>AF Number:</u>	5. <u>Supplement</u>
JAN - 6 1992			
6. <u>Name of Drug:</u> Prilosec	7. <u>Nonproprietary Name:</u> Omeprazole	Numbers SCM-008	Dates Jan 17, 1991
8. <u>Supplement Provides for:</u> changing the manufacturing site from Sweden to West Point, PA and Kirkland, Canada		9. <u>Amendments and Other (Reports, etc.) Dates:</u> AC July 1, 1991 AC December 13, 1991	
10. <u>Pharmacological Category:</u> Anti-ulcer	11. <u>How Dispensed:</u> RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. <u>Related IND/NDA/DMF(s):</u>	
13. <u>Dosage Form:</u> Delayed-release capsule	14. <u>Potency:</u> 20 mg		
15. <u>Chemical Name and Structure:</u> 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole		16. <u>Records and Reports:</u>	
		Current <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
		Reviewed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
17. <u>Comments:</u> The applicant has responded to the Agency's deficiency letter of November 21, 1991. See Review Notes cc: NDA 19-810 HFD-180/Div File HFD-181/CSO HFD-180/SFredd HFD-180/AShaw/December 20, 1991 R/D init by: JGibbs/12-30-91 typist: AS/dob/f/t 1-3-91 Wp:19810112.0AS			
18. <u>Conclusions and Recommendations:</u> The applicant should be sent an Information Request letter.			
19. <u>Reviewer</u>			
Name: Arthur B. Shaw, Ph.D.	Signature <i>Arthur B. Shaw</i>	Date Completed: January 3, 1992	<i>JGibbs</i> 1/6/92

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 § 552(b)(5) Deliberative Process

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CHEMIST'S REVIEW #41. Organization: HFD-180		2. NDA Number: 19-810	
3. Name and Address of Applicant (City & State): Merck Sharp and Dohme West Point, PA 19486 Address		4. AF Number:	
DEC 31 1992		5. Supplement	
6. Name of Applicant: Prilosec		Numbers	Dates
[REDACTED]		SCM-008	Jan 17, 1991
8. Supplemental manufacturing information and Kirkland		9. Amendments and Other (Reports, etc.) Dates: AC July 1, 1991 AC December 13, 1991 C Mar 20, 1992 C Sep 1, 1992	
10. Pharmacological class: Anti-ulcer		12. Related IND/NDA/DMF(s):	
13. Dosage Form: Delayed-release			
15. Chemical Name and Structure: 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole		16. Records and Reports: Current <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
17. Comments: The applicant has responded to the Agency's approvable letter of January 7, 1992. See Review Notes cc: NDA 19-810 HFD-180/Div File HFD-181/CSO HFD-180/SFredd HFD-180/AShaw/ R/D init by: JGibbs/12-30-92 typist: AS/dob/f/t 12-30-92 Best Possible Copy Wp:c:\chem\I\19810008.4AS			
18. Conclusions and Recommendations: The applicant has provided sufficient data to support an expiration date of 18 months.			
19. Reviewer			
Name: Arthur B. Shaw, Ph.D.		Signature Arthur B. Shaw 12/30/92	Date Completed: December 30, 1992

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 § 552(b)(5) Deliberative Process

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-810 / S-008

**CLINICAL PHARMACOLOGY/
BIOPHARMACEUTICS REVIEW(S)**

JUL 24 1991

NDA 19-810 Suppl.
OMEPRAZOLE
Prilosec™ Enteric Coated 20 mg Capsules
(formerly Losec™)
Merck Sharp & Dohme

DATE OF SUBMISSION:
July 3rd, 1991.

REVIEWER: Lydia C. Kaus Boggs, MS, PhD

TYPE OF SUBMISSION: Supplement to NDA for change in manufacturing site.

SYNOPSIS:

In their 1/17/91 submission: the firm set out to show bioequivalence between omeprazole 20 mg capsules (Merck) and omeprazole 20 mg capsules (Astra), after a change in manufacturing site. The two formulations were shown to be bioequivalent falling within the 90% CI for the two one-sided t-test. However deviations in the final manufacturing process as described by the reviewing Chemist for HFD-180 have implications for the conclusions drawn from the bioequivalence study in this submission. The firm has submitted 7/3/91 dissolution data, however full profiles (% dissolution at individual time points) were not provided and dissolution data at 50 rpm were not provided.

RECOMMENDATION:

In the Division of Biopharmaceutics' review dated 6/24/91 of the supplement to NDA 19-810, which described a bioequivalence study of omeprazole 20 mg capsules between two manufacturing sites, the Division recommended the following:

The firm has shown that the Lot used in the bioequivalence study for omeprazole 20 mg capsules (Merck) is bioequivalent to the omeprazole 20 mg capsules (Astra). However this Lot is not representative of a lot which has undergone the firm's proposed final manufacturing procedure. Experience has shown that this type of modified release has inherent problems with variability and *in vivo* characterization is essential; a bioequivalence study, which compares omeprazole 20 mg capsules (Astra) to omeprazole 20 mg capsules (Merck) would be preferred, however the firm has been requested to submit dissolution data of the lots used in the bioequivalence study and a recent full production lot. The Division of Biopharmaceutics will defer its final decision once this data has been reviewed.

The firm has submitted 7/3/91 dissolution data, however full profiles (% dissolution at individual time points) were not provided and dissolution data at 50 rpm were not provided. These requests were written in a letter to the firm from Dr. Fredd dated July 10, 1991. The Division will wait to review the data as requested in the letter which will cover the information supplied in this submission.

CV *Boggs*
7/17/91
Lydia C. Kaus Boggs, MS PhD
Reviewer, Division of Biopharmaceutics

RD Initialed by John Hunt

Ft Initialed by John Hunt

JH 7/19/91
JH 7/19/91

cc NDA 19-810 (Suppl), HFD-180, HFD-426 (Kaus Boggs), Chron, Drug, FOI, Reviewer files.

LCKB:PC:N19-801:7/17/91.

NDA 19-810 Suppl.
OMEPRAZOLE
Prilosec™ Enteric Coated 20 mg Capsules
(formerly Losec™)
Merck Sharp & Dohme

DATE OF SUBMISSION:
January 17th, 1991.

JUN 24 1991

REVIEWER: Lydia C. Kaus Boggs, MS, PhD

TYPE OF SUBMISSION: Supplement to NDA for change in manufacturing site.

SYNOPSIS:

The firm set out to show bioequivalence between omeprazole 20 mg capsules (Merck) and omeprazole 20 mg capsules (Astra), after a change in manufacturing site. The two formulations were shown to be bioequivalent falling within the 90% CI for the two one-sided t-test. However deviations in the final manufacturing process as described by the reviewing Chemist for HFD-180 have implications for the conclusions drawn from the bioequivalence study in this submission.

RECOMMENDATION:

The Division of Biopharmaceutics has reviewed the supplement to NDA 19-801⁵⁸, which describes a bioequivalence study of omeprazole 20 mg capsules between two manufacturing sites. The firm has shown that the Lot used in the bioequivalence study for omeprazole 20 mg capsules (Merck) is bioequivalent to the omeprazole 20 mg capsules (Astra). However this Lot is not representative of a lot which has undergone the firm's proposed final manufacturing procedure. Experience has shown that this type of modified release has inherent problems with variability and *in vivo* characterization is essential; a bioequivalence study, which compares omeprazole 20 mg capsules (Astra) to omeprazole 20 mg capsules (Merck) would be preferred, however the firm has been requested to submit dissolution data of the lots used in the bioequivalence study and a recent full production lot. The Division of Biopharmaceutics will defer its final decision once this data has been reviewed. The comments (1-6) and conclusions (1 & 2) should be sent to the firm.



Background:

Omeprazole is currently approved as an enteric-coated formulation as 20 mg capsules. The purpose of this supplemental submission to NDA 19-810 is to show bioequivalence between omeprazole granules currently manufactured by Astra, Sweden and encapsulated by Merck Sharp & Dohme (US) to omeprazole granules to be manufactured by Merck Frosst, Canada and Merck at West Point, PA with final encapsulation by Merck at West Point, PA. Also some concerns were raised about the dissolution method in the review of the original NDA, which the firm has addressed in this supplemental submission.

Comments:

1. The firm does not adequately document how the Lot # C-W281 (Merck) relates to Lot# A 210418 described in the manufacturing record.
2. Several deviations in the manufacturing procedure have been brought to the Division's attention by the reviewing Chemist for this submission. Please refer to the Letter sent out by HFD-180 to the firm dated May 29th, 1991. These deviations concern the Lot used in this study and therefore this Lot #A214018 is not representative of the final manufacturing procedure. Specific manufacturing deviations, which may affect the bioequivalence study are

3. The capsules selected for the bioequivalence study were subjected to a weight screening of $\pm 2.5\%$. The Division requests that capsules used in future bioequivalence study should be a random selection and not subject to a weight screen.
4. As an interim policy the test batch for bioequivalence studies where there has been a change in site should be 10% of the proposed production batch or 100,000 units, whichever is the greater.
5. No dissolution results for twelve representative units from the Merck nor the Astra Lots used in the study were provided. The firm has been requested to forward this dissolution data along with that of a recent full production lot (see attached memo of 'phone conversation with Dr. Molt 6/11/91).
6. The firm should also submit dissolution data at a paddle speed of 50 rpm for all the lots requested in Comment #5. This request was also made by Dr. Parekh in the November 19, 1990 meeting with the firm. Currently the firm uses a paddle speed of ' ' rpm, which has not been shown to the Division to be discriminatory with other products.

Conclusions:

1. The firm has shown that omeprazole 20 mg capsules (Merck) as processed by a deviation in the specified manufacturing process are bioequivalent to omeprazole 20 mg capsules (Astra).
2. The Lot used in study #021 is not representative of a lot which has undergone the firm's proposed final manufacturing procedure and therefore a bioequivalence study is preferred which

compares omeprazole 20 mg capsules (Astra) to omeprazole 20 mg capsules (Merck). However any final decision made will be deferred until the firm submits the requested dissolution data (see Comments #5 and 6).

Lydia C. Kaus Boggs
6/24/91

Lydia C. Kaus Boggs, MS PhD
Reviewer, Division of Biopharmaceutics

RD Initialed by John Hunt *JPH 6/21/91*
Ft Initialed by John Hunt *JPH 6/25/91*

cc NDA 19-801 (Suppl), HFD-180, HFD-426 (Kaus Boggs), Chron, Drug, FOI, Reviewer files.

LCKB:PC:N19-801:6-10-91,6/24/91.

Review of Study:

AN OPEN RANDOMIZED TWO PERIOD CROSSOVER STUDY TO DETERMINE THE BIOEQUIVALENCE OF 20 MG OMEPRAZOLE CAPSULES MANUFACTURED BY MERCK AND ASTRA.

Objective:

To determine whether omeprazole 20 mg capsules manufactured by Merck (new site) are bioequivalent to omeprazole 20 mg capsules manufactured by Astra (former site).

Investigator:

Drug Supplies:

Treatment A: Omeprazole 20 mg Capsules	Lot# C-W281	Merck Sharp & Dohme, PA Merck Frosst, Canada.
Treatment B: Omeprazole 20 mg Capsules	Lot# C-W282	Astra Pharm., Sweden

Subjects:

25 normal, healthy, male subjects were used. One subject withdrew for personal reasons and was replaced. Their mean age was 25.6 years of age (± 5.2), their mean weight was 165.9 lb (± 15.7) and their mean height was 69.5" (± 2.59).

Study Design:

This was an open-label, randomized two-period cross-over study. Each subject received each of two treatments with a minimum washout period of four days. The subjects fasted overnight prior to dosage administration and remained fasted for four hours post-administration.

Blood Sampling:

Blood was collected via an indwelling catheter into an arm vein at the following times: 20, 40 minutes, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours postdose.

Analytical Methodology:

The assay was previously validated in the original NDA. The following information was provided in this submission:

Assay Range: 10-500 ng/mL.

The reproducibility and precision of the method was shown by the intra- and inter-day variability data.

Intra-Day Variability for Assay Standards:

%CV range = 1.5%-9.3%.

9.3% was for the lowest standard (10 ng/mL)

Intra-Day Variability for QC Standards:

QC (low, 25 ng/mL)=3.2% (n=6)
 QC (high, 250 ng/mL)=2.0% (n=6)

Inter-Day Variability for QC Standards (calculated concentration):

QC(low, 26.59 ng/mL)=8.8% n=20
 QC(high, 264.26 ng/mL)=5.3% n=20

The assay is linear: A standard curve was shown with $r^2=0.9998$

Specificity was shown in the original NDA and also by representative chromatograms provided in this submission.

Sensitivity: The LOQ in plasma was / — /

Overall the assay is acceptable with regard to linearity, reproducibility, precision, sensitivity and specificity.

Pharmacokinetic and statistical analyses:

Log transformed values were used in the statistical analyses of AUC and C_{max} .

Table I Statistical and Pharmacokinetic Analyses of Omeprazole

Pharmacokinetic Parameter	Geometric Mean		p-value	90% CI	2 one sided t-test
	MERCK	ASTRA			
AUC (ng.h/mL)	359.2	356.2	0.84	94-109%	BE
C_{max} (ng/mL)	220.2	237.0	0.38	80-108%	BE
T_{max} (h)	Arithmetic Mean		0.20		
	1.6	1.4			

T_{max} Comparison of Individual Values:

Treatment Comparison	Earlier	Time Later	Same
Merck/Astra	25%	63%	13%

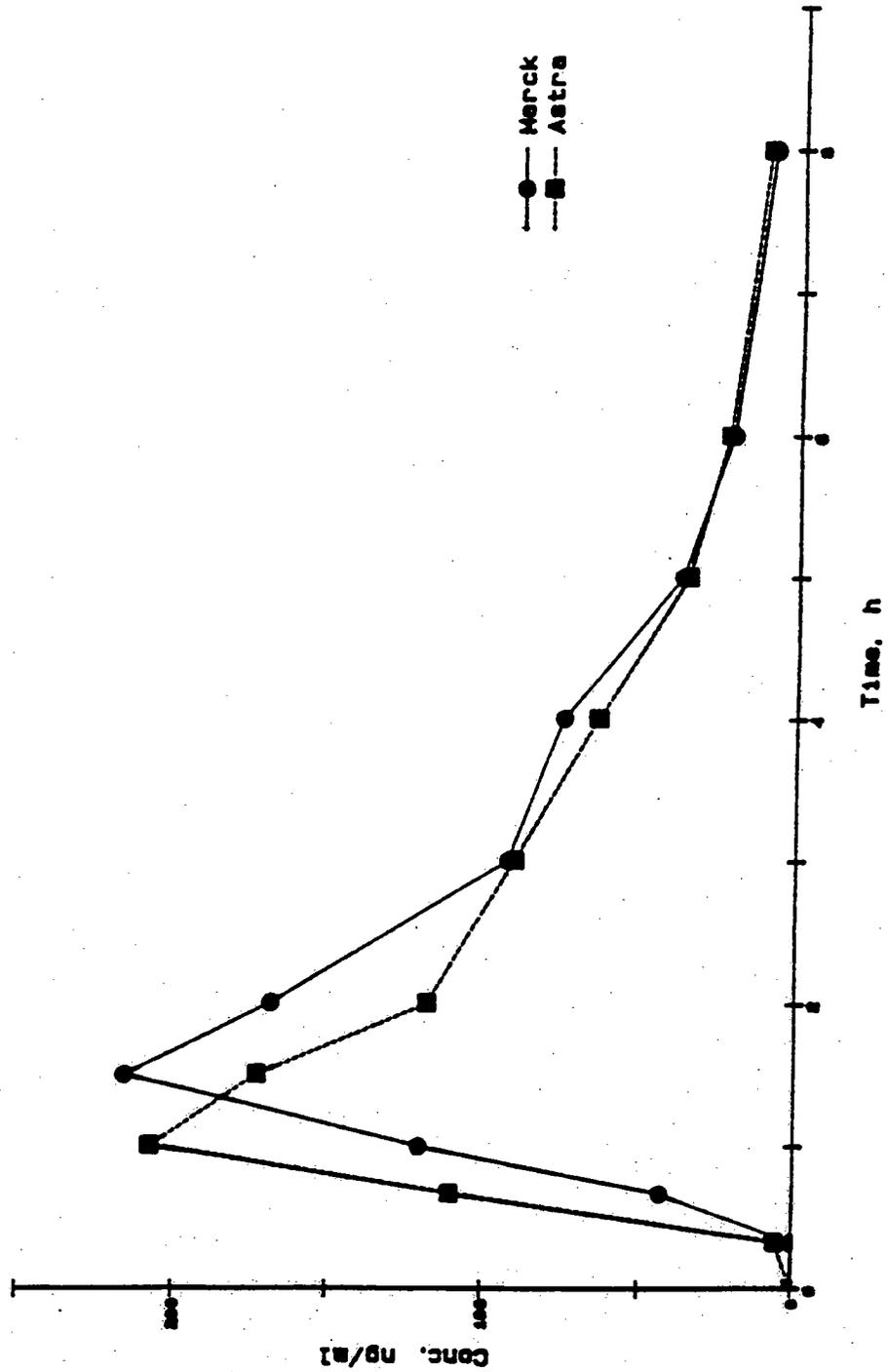
The omeprazole 20 mg capsules (Merck) although not statistically significantly different showed that in 63% of the subjects the time to peak plasma concentration was longer than omeprazole 20 mg capsules (Astra).

The bioequivalence study #015 was not reviewed since the firm stated that the lot manufactured by Merck was less than optimal in that the subcoating of the granules was uneven.

**Appears This Way
On Original**

Figure 3

Mean Plasma Profiles of Omeprazole
Following Single Oral Doses of PRILOSEC 20 mg
(M.A. #021-01, D.M. #845)

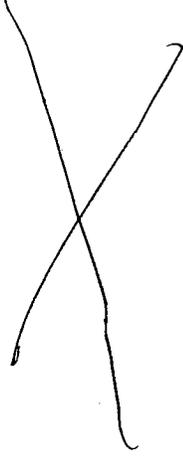


RAW DATA FOR TMAX IN STUDY omeprazole#21

TRT A IS astra
TRT B IS merck

SUBJECT

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
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- 13
- 14
- 15
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- 21
- 22
- 23
- 24



MEAN	1.347917	1.618333
%CV	53.89787	43.29607
N	24	24

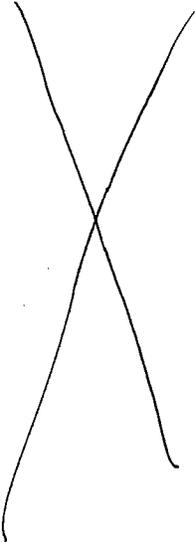
RESULTS OF INTRASUBJECT TMAX COMPARISON IN STUDY omeprazole#21

TRT A IS astra
TRT B IS merck

REFERENCE =

SUBJECT

- 1
- 2
- 3
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- 11
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- 23
- 24



MEAN MEDIAN MODE RANGE

B-A 0.27 0.50 0.50

FOR B-A THE MODE REPRESENTED 8 / 24 OR 33.33334 % OF SUBJECTS

FOR B - A: TMAX DIFF.	NUMBER	% OF SUBJECTS	MEAN	RANGE
< 0	6 / 24	25 %	-1.06	
> 0	15 / 24	63 %	0.85	
= 0	3 / 24	13 %	0	

copy 427

NDA 19-810 Amend.
OMEPRAZOLE
Prilosec™ Enteric Coated 20 mg Capsules
(formerly Losec™)
Merck Sharp & Dohme

DATE OF SUBMISSION:
Sept. 5, 1991.

OCT 10 1991

REVIEWER: Lydia C. Kaus Boggs, MS, PhD

TYPE OF SUBMISSION: Amendment to supplement to NDA for change in manufacturing site. Dissolution data submitted.

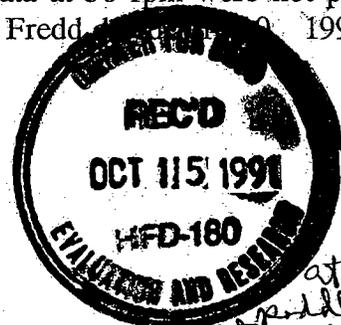
SYNOPSIS:

In their 1/17/91 submission: the firm set out to show bioequivalence between omeprazole 20 mg capsules (Merck) and omeprazole 20 mg capsules (Astra), after a change in manufacturing site. The two formulations were shown to be bioequivalent falling within the 90% CI for the two one-sided t-test. However deviations in the final manufacturing process as described by the reviewing Chemist for HFD-180 have implications for the conclusions drawn from the bioequivalence study in this submission. The firm has submitted 7/3/91 dissolution data, however full profiles (% dissolution at individual time points) were not provided and dissolution data at 50 rpm were not provided. The firm has responded to FDA requests from the reviewing Chemist and the Division of Biopharmaceutics. An expedited review is requested due to sole source.

In the Division of Biopharmaceutics' review dated 6/24/91 of the supplement to NDA 19-810, which described a bioequivalence study of omeprazole 20 mg capsules between two manufacturing sites, the Division recommended the following:

The firm has shown that the Lot used in the bioequivalence study for omeprazole 20 mg capsules (Merck) is bioequivalent to the omeprazole 20 mg capsules (Astra). However this Lot is not representative of a lot which has undergone the firm's proposed final manufacturing procedure. Experience has shown that this type of modified release has inherent problems with variability and *in vivo* characterization is essential; a bioequivalence study, which compares omeprazole 20 mg capsules (Astra) to omeprazole 20 mg capsules (Merck) would be preferred, however the firm has been requested to submit dissolution data of the lots used in the bioequivalence study and a recent full production lot. The Division of Biopharmaceutics chose to defer its final decision once this data was submitted.

The firm has submitted 7/3/91 dissolution data, however full profiles (% dissolution at individual time points) were not provided and dissolution data at 50 rpm were not provided. These requests were written in a letter to the firm from Dr. Fred... 1991 (copy attached).



10/17/91
Comments 1-4 to
affman

7/3/91
at recent meeting
1 RPM
paddle speed
held as approved. Hold commi
2 RPM. 51

RECOMMENDATION:

The Division has reviewed the amendment to the supplement for NDA 19-810 and found it to be lacking. Comments #1-4 should be forwarded to the firm. The Division looks forward to receiving the bioequivalency study comparing 20 mg capsule (Astra) to 20 mg capsules (Merck). The Division cannot set a final specification until adequate data has been provided by the firm and the firm must use a statistically valid test to show that there is no difference in dissolution between the Merck and Astra dissolution results.

DISSOLUTION ANALYSES:

CAPSULE #	% DISSOLUTION at 60 mins			
	50 RPM PADDLE SPEED			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
MEAN	89.3	83.1	88.1	80.4
%CV	4.1	3.1	4.0	3.1

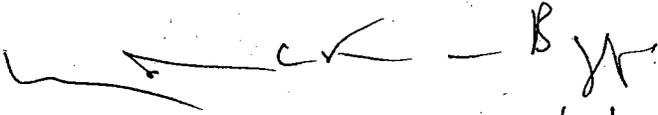
Individual dissolution profiles (% dissolved vs. time) were provided using 100 rpm paddle speed, but these were not provided for the lower speed of 50 rpm. These were the lots used in the bioequivalency study for approval of change in manufacturing site.

Comments:

1. The reviewer carried out ANOVA (see attached) of the above results and found that the dissolution was significantly different among groups. A post-hoc Duncan procedure showed that the mean for the Merck lot at the two paddle speeds at 60 minutes sampling time were not different at $p=0.05$ level, however the means for all other groups were different at this level. This suggests that the paddle speed made a difference to the dissolution results from the Astra capsules and that the Astra capsules' dissolution was different from that of the Merck capsules. The firm may want to carry out their own statistical analysis to show otherwise.
2. The firm did not provide % dissolved vs. time profiles for the Astra and Merck biolots at

50 rpm.

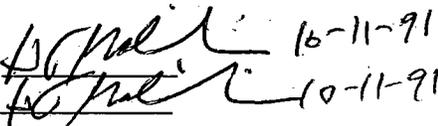
3. The firm has not shown that 50 rpm speed cannot be used in their dissolution specification.
4. The firm has not shown by a valid statistical test that the Merck and Astra dissolution results show no significant difference.


Lydia C. Kaus Boggs, MS PhD
Reviewer, Division of Biopharmaceutics

10/10/91

RD Initialed by Henry Malinowski, Ph.D.

FT Initialed by Henry Malinowski, Ph.D.


10-11-91

cc NDA 19-810 (Suppl), HFD-180, HFD-426 (Kaus Boggs), Chron, Drug, FOI, Reviewer files.

LCKB:PC:N19-810:10/3/91, 10/10/91.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-819/ S-008

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

orig. 457

MEMORANDUM OF TELECON

DATE: March 25, 1992

APPLICATION NUMBER: IND _____
NDA 19-810/S-008

BETWEEN:

Name: James T. Molt, Ph.D.
Phone: (215) 834-2306
Representing: Merck Sharp & Dohme Research Laboratories

AND

Name: Deborah Yaplee
Div. Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT:

Prilosec Delayed-Release Capsules/S-008, submission
dated March 20, 1992

~~_____~~

Prilosec Delayed-Release Capsules/S-008, submission dated
March 20, 1992

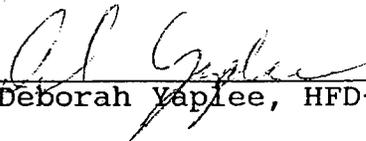
Background

This supplement provided a change in the manufacturing site to the U.S. and Canada. In the submission, the firm requested concurrence for an 18 month expiration dating for this drug product. I spoke with Dr. John Gibbs about the question. He stated the firm had received an 18 month expiration dating when the supplement had been approved (January 27, 1992).

I informed Dr. Molt that they had received an 18 month expiration dating when the supplement had been approved and did not understand why the firm was asking for concurrence for the 18 month expiration dating. He said their question had arisen from the January 7, 1992, approvable letter from the Division.

IND 32, 814
NDA 19-810/S-008
Telecon
Page2

Therefore, they were submitting this submission to support the 18 month expiration dating. I informed him I had spoken with the chemists to confirm the 18 month expiration dating for this product. He asked if he needed to submit this in writing. I said no because I would be writing a telecon and submitting it to the file. We then concluded the call.


Deborah Yaplee, HFD-180

cc:
IND 32,814
NDA 19-810/S-008
HFD-180/Division Files
HFD-180/DYaplee
HFD-180/JGibbs
HFD-180/SFredd
I\32814203.1DY

TOWB 3/25/92

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MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
WEST POINT, PENNSYLVANIA 19486

JAMES T. MOLT, Ph.D.
DIRECTOR
REGULATORY AFFAIRS

(215) 834-2306
(215) 661-5000

NEW CORRESPONDENCE

January 17, 1992

Dr. Stephen B. Fredd, Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Fredd:

NDA 19-810/S-008: PRILOSEC Delayed-Release Capsules
(Omeprazole)

Please refer to your letter dated January 7, 1992, received January 13, 1992, indicating that the above captioned supplement is approvable pending satisfactory cGMP inspection of the West Point, Pennsylvania and Kirkland, Canada facilities. You also request that we provide responses to 11 questions and stipulate that these responses may be provided now or after approval.

With this letter we wish to notify you of our intent to amend this application. We commit to provide answers to all questions after approval.

Please direct questions or need for additional information to James T. Molt, Ph.D. (Phone: 215-834-2306/Fax: 215-834-2335) or, in my absence, Elliott T. Berger, Ph.D. (Phone: 215/834-2310).

Sincerely yours,

James T. Molt
James T. Molt, Ph.D.

pka/5426G
Federal Express No. 0320237444

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not desk copies.

copy SMC-008
3/27/92
87
45/1

MERCK SHARP & DOHME RESEARCH LABORATORIES

DIVISION OF MERCK & CO. INC.
WEST POINT, PENNSYLVANIA 19486

ORIGINAL

JAMES T. MOLT, Ph.D.
DIRECTOR
REGULATORY AFFAIRS

March 20, 1992

(215) 834-2306
(215) 661-5000

Dr. Stephen B. Fredd, Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Fredd:

INFORMATION TO APPROVED SUPPLEMENT
EXPEDITED REVIEW REQUESTED

NDA 19-810/S-008: PRILOSEC Delayed-Release Capsules
(Omeprazole)

Please refer to an approvable letter for the above captioned supplement issued by your Division on January 7, 1992 which included requests for 11 items. The letter stipulated that the information requested could be supplied post approval. On January 27, 1992, NDA 19-810/S-008 was approved. We have provided you with a commitment to answer the 11 items. With this letter we wish to address item 10, as it deals specifically with expiration dating for the product. An expiration date needs to be established before material produced under the approved supplement can be released for marketing.

Item 10 of the January 7, 1992 letter stated:

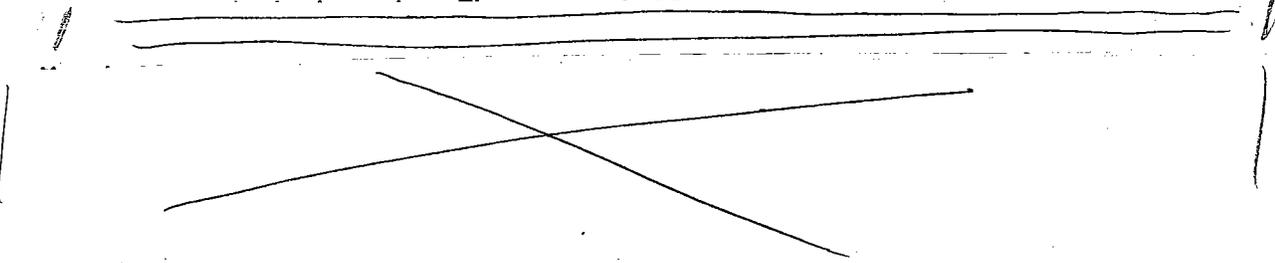
Submit stability data for three lots manufactured under the current procedure before an expiration date based on extrapolation of existing data can be calculated.

In addition, please be aware of the fact that stability data in the original submission (Page 3A00243) shows that Astra-manufactured material was stable at . While we recognize that this may be considered a stress condition, the fact that the Astra-manufactured material was stable under these conditions while the Merck-manufactured material is not is a sign that there is something different about the Merck-manufactured product. Therefore we will need to see more data before granting an expiration date based upon relatively short-term data at . This is particularly important because the dissolution specifications for the drug product are not stringent. You may wish to consider:

 for Merck-manufactured drug product.

Attachment 1 contains stability on three lots of Merck-manufactured material (manufactured under the current procedure) and, for comparison, one lot of Astra-manufactured material, on the same stability protocol. These data show no difference between the Astra material and the Merck material. Material from two of these lots (2001983 Astra and 2001940 Merck) are also on a "stressed" stability protocol. These data show no difference for all comparisons between the Merck material and the Astra material, even at these stressed conditions. Thus, these data support an expiration date for the Merck-manufactured material. As is our standard practice, commercial lots will be monitored throughout the expiry period. Merck will promptly investigate and withdraw, if appropriate, any lots that do not meet the approved specifications.

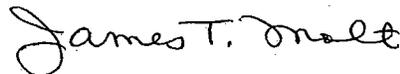
In your letter of January 7, 1992 you cite stability of Astra product at Please note that the referenced material, lot FBS 471, (page 3A00243) was packaged in with



We seek your concurrence that these data support an 18-month expiration dating for the Merck-manufactured material. As you are aware, the Merck-manufactured material needs to be made available soon in order to prevent shortages. As such, we request an expedited resolution on the expiration dating for this product.

Please direct questions or need for additional information to James T. Molt, Ph.D. (Phone: 215-834-2306/Fax: 215-834-2335) or, in my absence, Elliott T. Berger, Ph.D. (Phone: 215/834-2310).

Sincerely yours,



James T. Molt, Ph.D.

pka/5507G
Attachments
Federal Express No. 2994723756

Desk Copy:
Dr. John Gibbs, HFD-180, Rm. 6B45
Federal Express No. 2994723760

copy 441

MEMORANDUM OF TELECON

DATE: December 17, 1991

APPLICATION NUMBER: N19-810/S-008

BETWEEN:

Name: James Molt, Ph.D
Phone:
Representing: MSD

Best Possible Copy

AND

Name: Tom Hassall, SCSO
Div. Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Supplement for change of site of manufacture of Prilosec

Dr. Molt called with the following information concerning this supplement:

1. The supply of Prilosec continues to overwhelm demand. The firm is concerned there will be shortages of the product unless the new site can be cleared for production.
2. The firm responded to the Division's deficiency letter on December 13, 1991 (Agency letter date: 11/21/91). A desk copy was provided to Dr. Gibbs.
3. With respect to inspections: The West Point, PA facility was inspected and he understands it was given a "clean bill of health". The foreign inspection situation is more complex but his understanding is as follows:
 - a. International compliance (Peter Smith's office) made an arrangement with Canada that a prior acceptable Canadian inspection would suffice as a pre-approval inspection;
 - b. A letter is supposed to be issued from a Michael Hayes, Ottawa, Canada to Paul Vogel's office stating that the Canadian facility passed its previous Canadian inspection.
4. This supplement was submitted under the provisions for Expedited Review.

I told Dr. Molt we were aware of the supply issues with the product and were attending to the supplement promptly. I added that the inspection situation was difficult to get clear signals on but would convey his understanding to the review staff.

Thomas H. Hassall
Thomas H. Hassall

cc:NDA 19-810/S-008
HFD-180
HFD-180/CSO

HFD-180JGibbs

HFD-180/SFredd

12/23/91 Re Demand overwhelms supply, I presume. 171

09. 431

DEC 17 1991

NDA 19-810/S-008

Merck Sharp & Dohme Research Laboratories
Attention: James T. Molt, Ph.D.
West Point, PA 19486

Dear Dr. Molt:

Please refer to your December 13, 1991 amendment, received on December 16, 1991, to your supplemental new drug application for Prilosec (omeprazole) Delayed Release Capsules.

The amendment consisted of responses to the division's requests for additional information in our letter dated November 21, 1991 regarding your supplemental application for a change of manufacturing site for this product.

We consider this amendment major under 21 CFR 314.60 of the regulations. We acknowledge your request for expedited review of this supplement as amended. Please note, however, we have extended the due date to February 14, 1992.

If you have any questions, please contact:

Mr. Thomas H. Hassall
Supervisory Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 19-810/S-008
HFD-80/DDIR
HFD-180
HFD-181/CSO
DISTRICT OFFICE

thassall/December 17, 1991
th/December 17, 1991/C:\wp51\cso\N\19810112.0th

REVIEW EXTENSION

copy. 4/1/

NOV 21 1991

NDA 19-810/S-008

Merck Sharp and Dohme
Attention: James T. Molt, Ph.D.
West Point, Pennsylvania 19486

Dear Dr. Molt:

Please refer to your January 17, 1991 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Capsules, 20 mg.

The supplemental application provides for a change in manufacturing site to West Point, Pennsylvania and Kirkland, Canada.

We also acknowledge receipt of your amendment dated July 1, 1991.

Your application is currently under review and the following points need clarification:

A. Regarding the manufacturing procedure for:

f

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~~_____~~

L

]

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Nov. 21, 1999

NDA 19-810/SCM-008
PAGE 5

Should you have any questions, please contact:

Steven Budabin
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

John J. Gibbs, Ph. D.
Supervisory Chemist
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 19-810

HFD-180

HFD-181/CSO

HFD-180/SFredd

HFD-80/DDIR

HFD-180/AShaw/November 8, 1991 *ABS 11/21/91*

abs/dob/11/14/91/f/t11-21-91/Wp# 19810111.1AS

INFORMATION REQUEST

MEMORANDUM

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



DATE: OCT - 7 1991

FROM: Environmental Assessment Officer HFD-102

58

SUBJECT: Environmental Concerns--NDA 19-810 SNDA New Site of
Manufacture--Prilosec Delayed-Release Capsules
(Omeprazole) Stamp Date 17-JAN-91
SCM-008

TO: A. Shaw HFD-180

Merck, Sharp & Dohme

Merck, Sharp & Dohme is requesting an action from FDA for an expedited review request in subject Supplemental NDA. Approval of supplements to existing approvals of FDA-approved articles requires the preparation of an environmental assessment at § 25.22(a)(8), unless it qualifies for exclusion under §§ 25.23 and 25.24.

The Center has determined that an environmental assessment must be submitted for new sites of manufacture. The following is a suggested format for the environmental assessment:

ENVIRONMENTAL ASSESSMENT
(Supplements/Amendments NDE New Production Sites)
(Excipients/Change in Process)

1. Date
2. Name of applicant or petitioner:
3. Address:
4. Description of the proposed action: Briefly describe the requested action (i.e., approval of a new drug product); the location where the product will be produced; and the types of environments present at and adjacent to the location where the production will occur. Include a discussion of the proposed indications for use of the product, a proposed label, or a reference to the section of 21 CFR Part 314 that describes the

proposed conditions of use of the product.

5. Provide complete nomenclature, CAS Registry Number (if available), molecular weight, structural formulae, and physical description for the drug product to be produced. This information is required to allow accurate location of data about chemicals in the scientific literature and to allow identification of closely related chemicals.

6. Introduction of substances into the environment for the site(s) of production:

- a. list the substances expected to be emitted;
- b. state the controls exercised to modify emissions;
- c. describe the applicable emission requirements and permits obtained (including occupational) at the Federal, State and local level;
- d. provide a statement certifying compliance with all applicable emission requirements;
- e. discuss the effects the approval of this supplement/amendment will have upon compliance with current emissions requirements at the production site(s).

*See note below for optional alternative method for addressing this item available for foreign manufacturing sites.

7.-11. Documentation for items 7-11 of the EA format in 21 CFR 25.31a, concerning the fate, effects, resource and energy use, mitigation and alternatives, usually need not be provided for supplements/amendments for new production sites. Attach appropriate information for items 7 and 8 from the original environmental assessment.

Effects, if any, upon endangered or threatened species (16 U.S.C. 1536) and upon property listed in or eligible for listing in the National Register of Historic Places (16 U.S.C.470) must be discussed. Also the effects that are required under statutes or Executive Orders must be discussed in the NEPA review, consistent with 40 CFR 1502.25, the HHS General Administration Manual, Part 30, and 21 CFR 25.5(c)(1-16).

12. List of the preparers: List those persons who prepared the assessment together with their qualifications (expertise, experience, professional disciplines, etc.). Persons and agencies consulted should also be listed.

13. Certification: Include a statement signed by the responsible

official of the applicant's firm that certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm.

(Date): _____
(Signature of Responsible official): _____
(Title of responsible official): _____

14. References: List complete citations for all referenced material. Copies of referenced articles should be attached.

15. Appendices. Normally not needed for supplements/amendments. Attach appropriate information from the original environmental assessment.

*Alternative for item 6 when part or all of the manufacture is located in a foreign country.

It is a common and incorrect assumption that, because a product is manufactured in a foreign country, no environmental review of that aspect of the application is required. Under NEPA, Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", and 21 CFR 25.50, the requirement for evaluation of the impact of agency actions on the global commons and on foreign countries is established.

The preferred method for addressing item 6 of the above format is to provide the information requested, substituting the requirements of the foreign country where the manufacturing will occur for Federal, State and local emission requirements. Sometimes applicants have found that it is more convenient to obtain a letter or letters from the appropriate office(s) of the foreign government stating that the manufacture of the product that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug product that would be manufactured under the NDA and the government's requirements, such a letter can be used in lieu of the information requested in item 6a, b, c, and e, above.

The applicant may make reference to items 7 and 8 in their original environmental assessment as well as items 14 and 15 of their original environmental assessment for all the required fate and effects testing and the testing reporting requirements.

copy, 36.1

JAN 28 1991

NDA 19-810/S-008

Mark Sharp & Dohme Research Laboratories
Attention: James T. Molt, Ph.D.
West Point, Pennsylvania 19486

Dear Mr. Molt:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Prilosec (omeprazole) Delayed Release Capsules

NDA Number: 19-810

Supplement Number: S-008

Date of Supplement: January 17, 1991

Date of Receipt: January 17, 1991

The supplement provides for changing the manufacturing site of Prilosec (omeprazole) Delayed Release Capsules (20 mg) from Sweden to the United States and Canada.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on March 17, 1991 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal
and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM #10-74
5600 Fishers Lane
Rockville, Maryland 20857

Best Possible Copy

NDA 19-810

Page 2

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Mr. Steven E. Budabin
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 19-810

HFD-180

HFD-181/SBudabin

HFD-180/SBudabin/1/22/91

JW/1/22/91/5127d

SUPPLEMENT ACKNOWLEDGEMENT

SCS 1/22/91
Thank 1/28/91

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034 C (Reg. S-008 4) 52
11792 AE Miller

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
WEST POINT, PENNSYLVANIA 19486

ELLIOTT T. BERGER, PH.D.
SENIOR DIRECTOR
REGULATORY AFFAIRS

(215) 834-2310
(215) 661-5000

NEW CORRESPONDENCE

September 17, 1992



Dr. Stephen B. Fredd, Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

Dear Dr. Fredd:

NDA 19-810/S-008
PRILOSEC Delayed-Release Capsules
(Omeprazole)

Please refer to your approvable letter of January 17, 1992 and your subsequent approval letter of January 27, 1992 for the supplement to our New Drug Application NDA 19-810 for PRILOSEC Delayed Release Capsules (Omeprazole). This supplement provided for alternate manufacturing of omeprazole pellets in Kirkland, Canada and West Point, PA. With this letter we are providing responses to your January 17, 1992 comments.

1. Provide limits on the amount of _____ material in each batch.

Response: _____

2. Provide the data allowing the calculation of the yield specifications after _____ / soon they become available.

Response: _____

These yield specifications will be reviewed on an annual basis and may be adjusted in accordance with process capabilities.

Please refer to Attachment 1 for a listing of current yield data.

9/9/92

Dr. Stephen B. Fredd, Director
NDA 19-810/S-008: Delayed-Release Capsules PRILOSEC (Omeprazole)

3. Place specific references to, _____, SOP in the manufacturing batch record for the, _____.

4. Provide all of the data from the in-process tests.

Response: In addition to the previously provided in-process test results, the internal intermediate data are presented in Attachment 4. As indicated, these data are being provided for encapsulated lots 2001940, 2001941, and 2001942. Refer to Attachment 3 for the lot number assignments of _____ that were used in the manufacture of these three lots.

5. _____ in the future when a sufficient data base has been accumulated.

Response:

Please refer to the following information which indicates the status of the Internal Intermediate Specifications:

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3 Page(s) Withheld

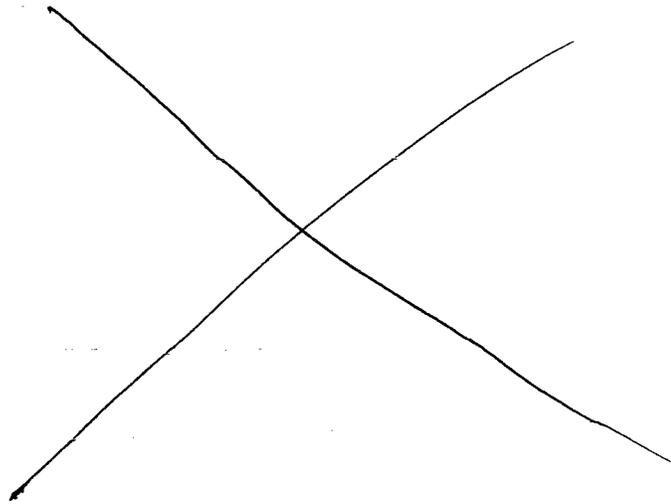
✓
 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

*Mueck
Sept 1, 1992*

Dr. Stephen B. Fredd, Director
NDA 19-810/S-008: Delayed-Release Capsules PRILOSEC (Omeprazole)



11. Specify the container/closure and the temperature on the stability report.

Response: We commit to provide a description of the container/closure and temperature on all future stability reports.

We consider the data supplied in this communication to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communication in regard to this topic, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be addressed to Elliott T. Berger, Ph.D. (215-834-2310), or in my absence to David W. Blois, Ph.D. (215-834-2304).

Sincerely yours,

Elliott T. Berger, Ph.D.

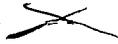
Information and data submitted herein contains trade secrets, or privileged or confidential information, the property of Merck & Co., Inc., and government agencies are not authorized to make it public without written permission from Merck.

ATTACHMENT 1

Comment 2

Yield Data

Enteric Coated Pellets



1 Page(s) Withheld

✓
 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

*Sept 1, 1992
proac
AD*

ATTACHMENT 2

Comment 3

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

March
April 1, 1992
#2

ATTACHMENT 3

Comment 4

Lot Number Assignments

— / Lots 2001940, 2001941, 2001942

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Mack
Apr 1 1992
3

ATTACHMENT 4

Comment 4

Internal Intermediate Test Results

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Muncie
Sept 1, 1992
4*

ATTACHMENT 5

Comment 6(a)

Spectrum (—) nm)
1.0% Omeprazole Standard Solution

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

*March
Sept 1, 1992
HS*

ATTACHMENT 6**Comment 6(b)****Plot: Omeprazole Concentration vs. Absorbance**

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

*March
Sept 1, 1992*

Included in this submission are the following:

Attachment I provides the mean values for drug release and acid resistance for the production batches (biobatch data are in Attachment III).

Attachment II are the individual data for acid resistance and drug release for the production batches.

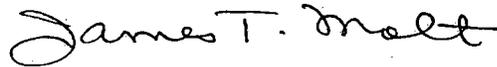
Attachment III shows the specific biobatch data for acid resistance and drug release for Merck and Astra formulations.

Attachment IV provides summary comparison of the Astra and Merck in vitro data.

Please note that while compiling this information it was noted that the formulation number which identified the Merck material used in the bioequivalence study was incorrect. The correct number is 7.
A corrected table is contained in Attachment V. This should replace the table on p. 6-00426 in the January 17, 1991 submission. We apologize for any inconvenience this may have caused.

Please direct questions or need for additional information to James T. Molt, Ph.D. (Phone: 215-834-2306/Fax: 215-834-2335) or, in my absence, Elliott T. Berger, Ph.D. (Phone: 215/834-2310/Fax: 215/834-2335).

Sincerely yours,



James T. Molt, Ph.D.

pka/5111G
Attachment
Federal Express No. 6673557203

Desk Copy with Attachment: Dr. Lydia Kaus-Boggs, HFD-426, Rm. 13B19
Federal Express No. 61673557214

Attachment 1

PRILOSEC® 20 MG DRUG RELEASE AND ACID RESISTANCE

Values For Control Chart (Averages of Six Unless Noted)

<u>RX NO.</u>	<u>DRUG RELEASE</u>	<u>ACID RESISTANCE</u>
1. 2001228	89.2%	94.4%
2. 2001229	90.4	93.7
3. 2001230	87.4	89.9
4. 2001231	85.3	94.4
5. 2001361	82.2	95.0
6. 2001359	82.2	93.1
7. 2001625	85.3	86.9 (n=12)
8. 2001624	86.7	87.2
9. 2001715	96.8	91.4
10. 2001716	83.6	87.6
11. 2001627	92.9	92.9
12. 2001802	96.3	96.4
13. 2001717	98.9	95.5
14. 2001939 Demo	85.2	85.1 (n=12)
15. 2001803	90.0	88.7
16. 2001804	90.4	90.1
17. 2001982	89.1	91.1
18. 2001983	86.0	87.4 (n=12)
19. 2001940 Validation #1	83.7 (n=12)	87.3 (n=12)
20. 2001984	86.0	84.0 (n=12)
21. 2002346	90.1	87.9 (n=12)
22. 2001941 Validation #2	82.5 (n=12)	85.9 (n=18)
23. 2002345	83.8	88.3 (n=12)
24. 2002347	87.0	93.1
25. 2002349	88.5	92.0
26. 2001942 Validation #3	85.4 (n=12)	87.6 (n=12)
27. 2002348	85.2	91.8
28. 2002350	88.3	92.9
29. 2002351	92.5	96.4

Lots marked Demo, Validation 1, 2, and 3 are Merck production batches. All others are Astra production batches. Data for the biobatches are in Attachment III.

Attachment 2

INDIVIDUAL VALUES FOR DRUG RELEASE AND ACID RESITANCE

11 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-July 8, 1991
#2

Attachment 3

1 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Attachment 4

PRILOSEC® 20 MG DRUG RELEASE & ACID RESISTANCE

Astra vs. Merck Data

	<u>No. Batches</u>	<u>Drug Release</u>	<u>Acid Resistance</u>
Astra Batch History	25	88.6%	91.4%
Merck Batch History	4	84.2	86.4
Merck Biobatch	1	88.2	93.1
Astra Biobatch (Used As The Control Batch in Bioequivalence Study)	1	85.0	87.8

revision.rjg

Attachment 5

1 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-

*March 3, 1991
5/14
A. H. H. H. H.
5*

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE

6/11/91

NDA NUMBER

19-810

IND NUMBER

TELECON MEETING

INITIATED BY

APPLICANT/
SPONSOR
 FDA

MADE

BY TELE-
PHONE
 IN PERSON

PRODUCT NAME

Omeprazole
20mg
Capsules

FIRM NAME

Merck Sharp
+ Dohme

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD

Dr Jim Molt
PHD

TELEPHONE NO.

215. 834-2306

Request for dissolution data
to be faxed on lots used
in Bioequiv Study # 021 (Astra
+ Merck)
and any recent production
lots.

SIGNATURE

[Signature] C. Kaus Begg

DIVISION

Biopharm.

ORIG 36.1

JUL 10 1991

NDA 19-810/S-008

Merck Sharp and Dohme Research Laboratories
Attention: James T. Molt, Ph.D.
West Point, PA 19486

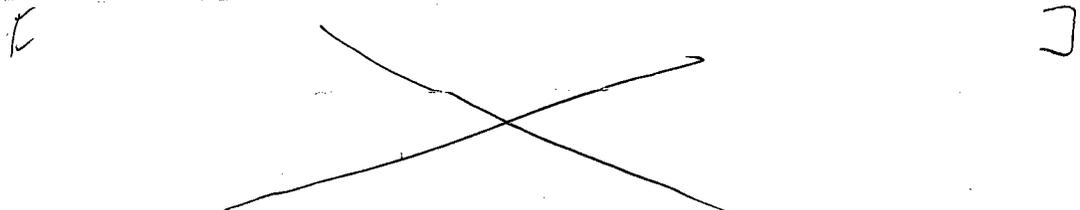
Dear Dr. Molt:

Please refer to your January 17, 1991 supplemental New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Capsules.

We also refer to our Not Approvable letter of May 29, 1991.

We have completed the biopharmaceutical review of your submission, and have the following recommendations and requests:

1. We do not consider lot # A214018 to be a representative sample of the final manufacturing procedure because of the following deviations which occurred, and which may affect the bioequivalence study:



As per our meeting of June 12, 1991 where we considered this issue, you agreed to perform dissolution testing on this lot and the currently marketed formulation (see 6). Additionally you should perform a bioequivalence study comparing omeprazole 20 mg capsules (Astra) to omeprazole 20 mg capsules (Merck) as soon as possible.

2. Please provide the in process control data for lot # A214018.
3. Please adequately document how lot # C-W281 (Merck) relates to lot # A214018 as described in the manufacturing record.
4. The capsules selected for the bioequivalence study were subjected to a weight screening of + 2.5%. Capsules used in future bioequivalence studies should be a random selection, and not subject to a weight screen.
5. As an interim policy, the test batch for bioequivalence studies in which a change in site has occurred, should be 10% of the proposed production batch or 100,000 units, whichever is greater.

Best Possible Copy

6. Please provide dissolution results for twelve representative units from the Merck and the Astra Lots used in the study.
7. We note that you currently use a paddle speed of 75 rpm, which has not been shown to be discriminatory with other products. Please submit dissolution data at a paddle speed of 50 rpm for all the lots requested in comment #6.

If you have any questions, please contact:

Steven Budabin
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig NDA 19-810/S-008
Div File
HFD-180/SBudabin
HFD-180/JGibbs
HFD-180/IKausboggs
HFD-180/SFredd
RD/INIT: JGibbs 7/5/91
THassall 7/3/91
SBudabin 7/3/91
SFredd 7/5/91
HFD-180/SBudabin/7/2/91
JW/7/2/91/5767d

INFORMATION REQUEST

SEB 7/9/91

BMA 7/9/91

SR 7/10/91

(sent 3 volumes)

13808

REQUEST FOR CONSULTATION

178

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division/Office) HFD-426 Biopharmaceutics

FROM: HFD-180

DATE 1-18-91 IND NO. NDA NO. 19-810 TYPE OF DOCUMENT SCM-008 DATE OF DOCUMENT 1-17-91

NAME OF DRUG PROLOSEC (Formerly LOSEC) (Concept: azole, MSD) PRIORITY CONSIDERATION CLASSIFICATION OF DRUG DESIRED COMPLETION DATE 3/18/91

NAME OF FIRM MERK SHARP & DOHME Recd. LAB.

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL, PROGRESS REPORT, NEW CORRESPONDENCE, DRUG ADVERTISING, ADVERSE REACTION REPORT, MANUFACTURING CHANGE/ADDITION, MEETING PLANNED BY, PRE-NDA MEETING, END OF PHASE II MEETING, RESUBMISSION, SAFETY/EFFICACY, PAPER NDA, CONTROL SUPPLEMENT, RESPONSE TO DEFICIENCY LETTER, FINAL PRINTED LABELING, LABELING REVISION, ORIGINAL NEW CORRESPONDENCE, FORMULATIVE REVIEW, OTHER (Specify below)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW, END OF PHASE II MEETING, CONTROLLED STUDIES, PROTOCOL REVIEW, OTHER, CHEMISTRY, PHARMACOLOGY, BIOPHARMACEUTICS, OTHER

III. BIOPHARMACEUTICS

ISSOLUTION

- BIOAVAILABILITY STUDIES, PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE, PROTOCOL- BIOPHARMACEUTICS, IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL, DRUG USE, CASE REPORTS OF SPECIFIC REACTIONS, COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP, REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY, SUMMARY OF ADVERSE EXPERIENCE, POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL, PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

In reference to our meeting with the firm on November 19, 1990, this supplement provides for a change in manufacturing site of 20 mg Prolosec Delayed Capsules from Sweden to the United States and Canada. This supplement includes biopharmaceutic and bioavailability data. Please review and return results to HFD-180. Thank you.



Handwritten initials/signature

HFD-180/ 443-0487

SIGNATURE OF REQUESTER: [Signature] CSO 1/18/91
SIGNATURE OF RECEIVER: E. Both

METHOD OF DELIVERY (Check one): MAIL, HAND
SIGNATURE OF DELIVERER: Roger J. Mellin

ag.

MEMORANDUM OF TELECON

DATE: April 23, 1991

APPLICATION NUMBER: NDA 19-810

BETWEEN:

Name: James T Molt, Ph.D
Phone: 215-834-2306
Representing: Merck Sharp and Dohme Research Laboratories

AND

Name: Steven E. Budabin, CSO
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

SUBJECT: Prilosec

I returned Dr. Molt's call responding to his previous inquiries from this morning regarding Prilosec. Dr. Molt asked about the status of NDA 19-810/S-008, the change in manufacturing site from Sweden to the United States, and--whether the Division would consider setting up a meeting to discuss the results of Dr. Solcia's re-reading of the gastric biopsy slides in order to determine the approval of Prilosec for their duodenal ulcer claim.

After consulting with Drs. Shaw and Gibbs, I discovered that the on site inspections (for both the West Point and Canadian facilities) will be initiated through our compliance office today. The chemists requested the firm to provide the exact building address of the manufacturing plant.

With respect to the firm's request for a meeting regarding their DU claim, Dr. Fredd requested that the firm submit their results for our review prior to scheduling any further meetings with Merck.

I conveyed the above information to Dr. Molt, and requested him to send us the West Point site address for the chemist's review.

Steven E. Budabin
Steven E. Budabin, CSO

CC:
NDA 19-810
Div File
HFD-180/SFredd
HFD-180/SBudabin

HFD-180/THassall

HFD-180/AShaw

HFD-180/JGibbs

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HFD-180/H Gallo-Torres

40-1

JUL 8 1991

NDA 19-810/S-008

Merck Sharp and Dohme Research Laboratories
Attention: James T. Molt, Ph.D
West Point, PA 19486

Dear Dr. Molt:

Please refer to your July 1, 1991 amendment, received on July 2, 1991, to your supplemental new drug application for Prilosec (omeprazole) Delayed Release Capsules. The supplemental application provides for changing the manufacturing site for Prilosec Capsules from Sweden to West Point, PA and Kirkland, Canada.

The amendment consisted of additional chemistry information in response to our not approvable letter of May 29, 1991.

We consider this amendment major under 21 CFR 314.60 of the regulations. We have determined that sixty (60) additional days will be required to complete our review of your application as amended. Accordingly, we have extended the due date to September 14, 1991.

If you have any questions, please contact:

Steven E. Budabin
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

cc:
Orig. NDA 19-810/S-008
HFD-80/DDIR
HFD-180
HFD-181/SBudabin
HFD-180/AShaw
HFD-180/THassall

RD/INIT: SBudabin 7/5/91

THassall 7/9/91

HFD-180/seb/7/5/91
seb/7/5/91/5784d

SGS 7/8/91

SF 7/8/91

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

REVIEW EXTENSION

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