

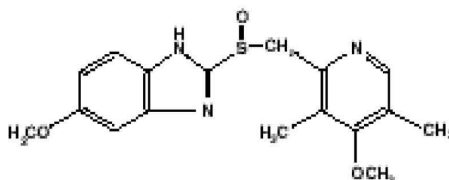
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PRILOSEC®
(OMEPRAZOLE)
DELAYED-RELEASE CAPSULES

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-

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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

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unknown.

The pharmacokinetics of omeprazole have been investigated in pediatric patients of different ages.

Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared to Adults

Single or Repeated Oral Dosing /Parameter	Children [†] < 20 kg 2-5 years 10 mg	Children [†] > 20 kg 6-16 years 20 mg	Adults [‡] (mean 76 kg) 23-29 years (n=12)
	Single Dosing		
C _{max} * (ng/mL)	288 (n=10)	495 (n=49)	668
AUC* (ng h/mL)	511 (n=7)	1140 (n=32)	1220
Repeated Dosing			
C _{max} * (ng/mL)	539 (n=4)	851 (n=32)	1458
AUC* (ng h/mL)	1179 (n=2)	2276 (n=23)	3352

Note: * = plasma concentration adjusted to an oral dose of 1 mg/kg.

[†]Data from single and repeated dose studies

[‡]Data from a single and repeated dose study

Doses of 10, 20 and 40 mg Omeprazole as Enteric-Coated Granules

Following comparable mg/kg doses of omeprazole, younger children (2-5 years) have lower AUCs than children 6 – 16 years or adults; AUCs of the latter two groups did not differ. (See DOSAGE AND ADMINISTRATION – Pediatric Patients.)

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}, AUC₀₋₂₄, 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 AUC₀₋₈ 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 AUC₀₋₈ was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations
2 hours after Dose[†]

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)

[†] Mean ± SD (µg/g)

MYL-EN000523847

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 H₂ 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 intra-gastric acidity in some patients.

MYL-EN000523848

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.) However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant 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.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of PRILOSEC 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed

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