

PRILOSEC - omeprazole magnesium capsule
STAT RX USA LLC

11 DESCRIPTION

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

STRUCTURE IMAGE

Omeprazole is a white to off-white crystalline powder that 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.

The active ingredient in PRILOSEC (omeprazole magnesium) for Delayed Release Oral Suspension, is 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, magnesium salt (2:1)

Omeprazole magnesium is a white to off white powder with a melting point with degradation at 200°C. The salt is slightly soluble (0.25 mg/ml) in water at 25°C, and it is soluble in methanol. The half-life is highly pH dependent.

The empirical formula for omeprazole magnesium is $(C_{17}H_{18}N_3O_3S)_2 Mg$, the molecular weight is 713.12 and the structural formula is

STRUCTURE IMAGE 2

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, hypromellose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin-NF, FD and C Blue #1, FD and C Red #40, D and C Red #28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD and C Blue #2, D and C Red #7 Calcium Lake, and, in addition, the 10 mg and 40 mg capsule shells also contain D and C Yellow #10.

Each packet of PRILOSEC For Delayed-Release Oral Suspension contains either 2.8 mg or 11.2 mg of omeprazole magnesium (equivalent to 2.5 mg or 10 mg of omeprazole), in the form of enteric-coated granules with the following inactive ingredients: glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer C, polysorbate, sugar spheres, talc, and triethyl citrate, and also inactive granules. The inactive granules are composed of the following ingredients: citric acid, crospovidone, dextrose, hydroxypropyl cellulose, iron oxide and xanthan gum. The omeprazole granules and inactive granules are constituted with water to form a suspension and are given by oral, nasogastric or direct gastric administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, 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.

12.2 Pharmacodynamics

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.

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.

Serum Gastric Effects

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

Enterochromaffin-like (ECL) Cell Effects

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 *Clinical Pharmacology* (12)] 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.

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 twice daily for 12 months followed by 20 mg twice daily for 12 months or ranitidine 300 mg twice daily 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 esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter [See *Clinical Pharmacology* (12)].

12.3 Pharmacokinetics

Absorption

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 with 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.

Based on a relative bioavailability study, the AUC and C_{max} of PRILOSEC (omeprazole magnesium) for Delayed-Release Oral Suspension were 87% and 88% of those for PRILOSEC Delayed-Release Capsules, respectively.

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

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.

Distribution

Protein binding is approximately 95%.

Metabolism

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system.

Excretion

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.

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.

Special Populations

Geriatric Population

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.

Pediatric Use

The pharmacokinetics of omeprazole have been investigated in pediatric patients 2 to 16 years of age:

Following comparable mg/kg doses of omeprazole, younger children (2 to 5 years of age) have lower AUCs than children 6 to 16 years of age or adults; AUCs of the latter two groups did not differ. [See *Dosage and Administration* (2)]

Hepatic Impairment

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

mL/min, compared with a value of 500-600 mL/min in normal subjects. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired should be considered.

Renal Impairment

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. No dose reduction is necessary in patients with renal impairment.

Asian Population

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared with Caucasians. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered.

12.4 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 (1.1).

Helicobacter

Helicobacter pylori- Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (4 and 5) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (1, 2, and 3).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (1, 2, and 3). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest[®].

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:

1 INDICATIONS AND USAGE

1.1 Duodenal Ulcer (adults)

PRILOSEC is indicated for short-term treatment of active duodenal ulcer in adults. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

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

PRILOSEC, in combination with clarithromycin is indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* in adults.

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence [see *Clinical Studies (14.1)* and *Dosage and Administration (2)*].

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 (12.4)*], and the clarithromycin package insert, Microbiology section.)

1.2 Gastric Ulcer (adults)

PRILOSEC is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer in adults. [See *Clinical Studies (14.2)*]

1.3 Treatment of Gastroesophageal Reflux Disease (GERD) (adults and pediatric patients)

Symptomatic GERD

PRILOSEC is indicated for the treatment of heartburn and other symptoms associated with GERD in pediatric patients and adults.

Erosive Esophagitis

PRILOSEC is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis that has been diagnosed by endoscopy in pediatric patients and adults. [See *Clinical Studies (14.4)*]

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, an additional 4 weeks of treatment may be given. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

1.4 Maintenance of Healing of Erosive Esophagitis (adults and pediatric patients)

PRILOSEC is indicated to maintain healing of erosive esophagitis in pediatric patients and adults.

Controlled studies do not extend beyond 12 months. [See *Clinical Studies (14.4)*]

1.5 Pathological Hypersecretory Conditions (adults)

PRILOSEC is indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis) in adults.

4 CONTRAINDICATIONS

PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria [see *Adverse Reactions (6)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with PRILOSEC Monotherapy

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed

in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to PRILOSEC Delayed-Release Capsules in 3096 patients from worldwide clinical trials (465 patients from US studies and 2,631 patients from international studies). Indications clinically studied in US trials included duodenal ulcer, resistant ulcer, and Zollinger-Ellison syndrome. The international clinical trials were double blind and open-label in design. The most common adverse reactions reported (i.e., with an incidence rate greater or equal to 2%) from PRILOSEC-treated patients enrolled in these studies included headache (6.9%), abdominal pain (5.2%), nausea (4.0%), diarrhea (3.7%), vomiting (3.2%), and flatulence (2.7%).

Additional adverse reactions that were reported with an incidence $\geq 1\%$ included acid regurgitation (1.9%), upper respiratory infection (1.9%), constipation (1.5%), dizziness (1.5%), rash (1.5%), asthenia (1.3%), back pain (1.1%), and cough (1.1%).

The clinical trial safety profile in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

The clinical trial safety profile in pediatric patients who received PRILOSEC Delayed-Release Capsules was similar to that in adult patients. Unique to the pediatric population, however, adverse reactions of the respiratory system were most frequently reported in both the 1 to greater than 2 and 2 to 16 year age groups (75.0% and 18.5%, respectively). Similarly, fever was frequently reported in the 1 to 2 year age group (33.0%) and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%). [See *Use in Specific Populations* (8.4)]

6.2 Clinical Trials Experience with PRILOSEC in 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 reactions unique to these drug combinations were observed. Adverse reactions observed were limited to those previously reported with omeprazole, clarithromycin, or amoxicillin alone.

Dual Therapy (PRILOSEC/clarithromycin)

Adverse reactions observed in controlled clinical trials using combination therapy with PRILOSEC and clarithromycin (n = 346) that differed from those previously described for PRILOSEC 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 prescribing information, Adverse Reactions section).

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)

The most frequent adverse reactions 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 antimicrobial agents alone. (For more information on clarithromycin or amoxicillin, refer to the respective prescribing information, Adverse Reactions sections).

6.3 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of PRILOSEC Delayed-Release Capsules. Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their actual frequency or establish a causal relationship to drug exposure.

Body As a Whole: Hypersensitivity reactions including anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, urticaria, (see also *Skin* below); fever; pain; fatigue; malaise;

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

Endocrine: Gynecomastia

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, 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. Gastroduodenal 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: Liver disease including hepatic failure (some fatal), liver necrosis (some fatal), hepatic encephalopathy hepatocellular disease, cholestatic disease, mixed hepatitis, jaundice, and elevations of liver function tests [ALT, AST, GGT, alkaline phosphatase, and bilirubin]

Metabolic/Nutritional: Hypoglycemia, hyponatremia, weight gain

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

Nervous System/Psychiatric: Psychiatric and sleep disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, and dream abnormalities; tremors, paresthesia; vertigo

Respiratory: Epistaxis, pharyngeal pain

Skin: Severe generalized skin reactions including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; photosensitivity; urticaria; rash; skin inflammation; pruritus; petechiae; purpura; alopecia; dry skin; hyperhidrosis

Special Senses: Tinnitus, taste perversion

Ocular: Optic atrophy, anterior ischemic optic neuropathy, optic neuritis, dry eye syndrome, ocular irritation, blurred vision, double vision

Urogenital: Interstitial nephritis, hematuria, proteinuria, elevated serum creatinine, microscopic pyuria, urinary tract infection, glycosuria, urinary frequency, testicular pain

Hematologic: Agranulocytosis (some fatal), hemolytic anemia, pancytopenia, neutropenia, anemia, thrombocytopenia, leukopenia, leucocytosis

5. WARNINGS AND PRECAUTIONS

5.1 Concomitant Gastric Malignancy

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

5.2 Atrophic Gastritis

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

5.3 Combination Use of PRILOSEC with 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.

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.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

5.4 Combination Use of PRILOSEC with 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.)

Co-administration of omeprazole and clarithromycin has resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. [See *Clinical Pharmacology* (12)]

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

10 OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. [See *Adverse Reactions* (6)] Symptoms were transient, and no serious clinical outcome has been reported when PRILOSEC was taken alone. 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.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, contact a Poison Control Center at 1-800-222-1222.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

2 DOSAGE AND ADMINISTRATION

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

Patients should be informed that the PRILOSEC Delayed-Release Capsule should be swallowed whole.

For patients unable to swallow an intact capsule, alternative administration options are available. [See *Dosage and Administration* (2.8)]

2.1 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.

2.2 *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 three times daily 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.

2.3 Gastric Ulcer

The recommended adult oral dose is 40 mg once daily for 4-8 weeks.

2.4 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.

2.5 Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily. [*See Clinical Studies (14.4)*]

2.6 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 daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg three times daily 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.

2.7 Pediatric Patients

For the treatment of GERD and maintenance of healing of erosive esophagitis, the recommended daily dose for pediatric patients— 1 to 16 years of age is as follows:

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis in pediatric patients are greater than those for adults.

Alternative administrative options can be used for pediatric patients unable to swallow an intact capsule [*See Dosage and Administration (2.8)*].

2.8 Alternative Administration Options

PRILOSEC is available as a delayed-release capsule or as a delayed-release oral suspension.

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.

PRILOSEC For Delayed-Release Oral Suspension should be administered as follows:

- Empty the contents of a 2.5 mg packet into a container containing 5 mL of water.
- Empty the contents of a 10 mg packet into a container containing 15 mL of water.
- Stir
- Leave 2 to 3 minutes to thicken.
- Stir and drink within 30 minutes.
- If any material remains after drinking, add more water, stir and drink immediately.

For patients with a nasogastric or gastric tube in place:

- Add 5 mL of water to a catheter tipped syringe and then add the contents of a 2.5 mg packet (or 15 mL of water for the 10 mg packet). It is important to only use a catheter tipped syringe when administering PRILOSEC through a nasogastric tube or gastric tube.
- Immediately shake the syringe and leave 2 to 3 minutes to thicken.
- Shake the syringe and inject through the nasogastric or gastric tube, French size 6 or larger, into the stomach within 30 minutes.
- Refill the syringe with an equal amount of water.

- Shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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 0186-0742-82 bottles of 1000.

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

PRILOSEC For Delayed-Release Oral Suspension, 2.5 mg or 10 mg, is supplied as a unit dose packet containing a fine yellow powder, consisting of white to brownish omeprazole granules and pale yellow inactive granules. PRILOSEC unit dose packets are supplied as follows:

NDC 0186-0625–01 unit dose packages of 30: 2.5 mg packets

NDC 0186-0610–01 unit dose packages of 30: 10 mg packets

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).

Store PRILOSEC For Delayed-Release Oral Suspension at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

PRILOSEC should be taken before eating. Patients should be informed that the PRILOSEC Delayed-Release Capsule 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.

PRILOSEC For Delayed-Release Oral Suspension should be administered as follows:

- Empty the contents of a 2.5 mg packet into a container containing 5 mL of water.
- Empty the contents of a 10 mg packet into a container containing 15 mL of water.
- Stir
- Leave 2 to 3 minutes to thicken.
- Stir and drink within 30 minutes.
- If any material remains after drinking, add more water, stir and drink immediately.

For patients with a nasogastric or gastric tube in place:

- Add 5 mL of water to a catheter tipped syringe and then add the contents of a 2.5 mg packet (or 15 mL of water for the 10 mg packet). It is important to only use a catheter tipped syringe when

administering PRILOSEC through a nasogastric tube or gastric tube.

- Immediately shake the syringe and leave 2 to 3 minutes to thicken.
- Shake the syringe and inject through the nasogastric or gastric tube, French size 6 or larger, into the stomach within 30 minutes.
- Refill the syringe with an equal amount of water.
- Shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

PRILOSEC is a trademark of the AstraZeneca group of companies.

©AstraZeneca 2008

Manufactured for: AstraZeneca LP, Wilmington, DE 19850

PRILOSEC For Delayed-Release Oral Suspension is a Product of Sweden

91941XX

31090-XX



LABEL IMAGE

PRILOSEC

omeprazole magnesium capsule

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:16590-334(NDC:0186-0742) |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|----------------------|----------|
| OMEPRAZOLE MAGNESIUM (UNII: 426QFE7XLK) (OMEPRAZOLE MAGNESIUM - UNII:426QFE7XLK) | OMEPRAZOLE MAGNESIUM | 20 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|------------------------------------|----------|
| FD&C BLUE NO. 2 (UNII: L06K8R7DQK) | |

Product Characteristics

| | | | |
|-----------------|--------------------------------|---------------------|--------------------------|
| Color | purple (AMETHYST) | Score | score with uneven pieces |
| Shape | CAPSULE (OPAQUE, HARD GELATIN) | Size | 17mm |
| Flavor | | Imprint Code | 742;prilosec20 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|-------------------------|----------------------|--------------------|
| 1 | NDC:16590-334-30 | 30 in 1 BOTTLE, PLASTIC | | |
| 2 | NDC:16590-334-60 | 60 in 1 BOTTLE, PLASTIC | | |
| 3 | NDC:16590-334-90 | 90 in 1 BOTTLE, PLASTIC | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA019810 | 09/30/2009 | |

Labeler - STAT RX USA LLC (786036330)

Revised: 2/2010

STAT RX USA LLC