

OMEPRAZOLE- omeprazole capsule, delayed release
RedPharm Drug, Inc.

1 INDICATIONS AND USAGE

1.1 Duodenal Ulcer (adults)

Omeprazole delayed-release capsules, USP are 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.

Omeprazole delayed-release capsules, USP, 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* in adults.

Omeprazole delayed-release capsules, USP, in combination with clarithromycin are 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, omeprazole delayed-release capsules with clarithromycin are 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)

Omeprazole delayed-release capsules, USP are indicated for short-term treatment (4 to 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

Omeprazole delayed-release capsules, USP are indicated for the treatment of heartburn and other symptoms associated with GERD in pediatric patients and adults for up to 4 weeks.

Erosive Esophagitis

Omeprazole delayed-release capsules, USP are indicated for the short-term treatment (4 to 8 weeks) of erosive esophagitis that has been diagnosed by endoscopy in pediatric patients and adults [see CLINICAL STUDIES (14.4)].

The efficacy of omeprazole delayed-release capsules, USP 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 to 8 week courses of omeprazole may be considered.

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

Omeprazole delayed-release capsules, USP are 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)

Omeprazole delayed-release capsules, USP are indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic

mastocytosis) in adults.

2 DOSAGE AND ADMINISTRATION

Omeprazole delayed-release capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with omeprazole.

Patients should be informed that the omeprazole 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 omeprazole delayed-release capsules 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 (omeprazole/clarithromycin/amoxicillin)

The recommended adult oral regimen is omeprazole delayed-release capsules 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 omeprazole delayed-release capsules 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (omeprazole/clarithromycin)

The recommended adult oral regimen is omeprazole delayed-release capsules 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 omeprazole delayed-release capsules 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 to 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. Controlled studies do not extend beyond 12 months [SEE CLINICAL STUDIES (14.4)].

2.6 Pathological Hypersecretory Conditions

The dosage of omeprazole delayed-release capsules 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 omeprazole delayed-release capsules 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 2 to 16 years of age is as follows:

Patient Weight Omeprazole Daily Dose

10 < 20 kg

10 mg

≥ 20 kg

20 mg

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

Omeprazole is available as a delayed-release capsule.

For patients who have difficulty swallowing capsules, the contents of an omeprazole 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.

3 DOSAGE FORMS AND STRENGTHS

Omeprazole delayed-release capsules, USP 10 mg are hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. "APO 010" is imprinted on each capsule in black ink.

Omeprazole delayed-release capsules, USP 20 mg are hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. "APO 020" is imprinted on each capsule in black ink.

Omeprazole delayed-release capsules, USP 40 mg are hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. "APO 040" is imprinted on each capsule in black ink.

4 CONTRAINDICATIONS

Omeprazole delayed-release capsules are contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [SEE ADVERSE REACTIONS (6)].

For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with omeprazole, refer to the CONTRAINDICATIONS section of their package inserts.

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 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops [see CONTRAINDICATIONS (4)].

5.4 Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.5 Clostridium difficile associated diarrhea

Published observational studies suggest that PPI therapy like omeprazole may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see ADVERSE REACTIONS (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with omeprazole, refer to WARNINGS AND PRECAUTIONS sections of those package inserts.

5.6 Interaction with Clopidogrel

Avoid concomitant use of omeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as omeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using omeprazole, consider alternative anti-platelet therapy [see DRUG INTERACTIONS (7.3) and PHARMACOKINETICS (12.3)].

5.7 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see DOSAGE AND ADMINISTRATION (2) and ADVERSE REACTIONS (6.3)].

5.8 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see ADVERSE REACTIONS (6.3)].

5.9 Concomitant Use of Omeprazole with St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease omeprazole concentrations [see DRUG INTERACTIONS (7.3)]. Avoid concomitant use of omeprazole with St. John's Wort or rifampin.

5.10 Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop omeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

5.11 Concomitant use of Omeprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [see DRUG INTERACTIONS (7.7)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with Omeprazole 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 omeprazole 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 $\geq 2\%$) from omeprazole-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 omeprazole 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 the 2 to 16 year age group (18.5%). Similarly, 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 Omeprazole in Combination Therapy for H. pylori Eradication

In clinical trials using either dual therapy with omeprazole and clarithromycin, or triple therapy with omeprazole, 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 (omeprazole/clarithromycin)

Adverse reactions observed in controlled clinical trials using combination therapy with omeprazole and

clarithromycin (n = 346) that 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 prescribing information, Adverse Reactions section).

Triple Therapy (omeprazole/clarithromycin/amoxicillin)

The most frequent adverse reactions observed in clinical trials using combination therapy with omeprazole, 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 omeprazole 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, microscopic colitis. 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 omeprazole. 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]

Infections and Infestations

Clostridium difficile associated diarrhea

Metabolism and Nutritional disorders

Hypoglycemia, hypomagnesemia, with or without hypocalcemia and/or hypokalemia, hyponatremia, weight gain

Musculoskeletal

Muscle weakness, myalgia, muscle cramps, joint pain, leg pain, bone fracture

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

7 DRUG INTERACTIONS

7.1 Interference with Antiretroviral Therapy

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19.

Reduced concentrations of atazanavir and nelfinavir

For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice

daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended.

Increased concentrations of saquinavir

For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with omeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

7.2 Drugs for Which Gastric pH Can Affect Bioavailability

Due to its effects on gastric acid secretion, omeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with omeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Co-administration of digoxin with omeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with omeprazole.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving omeprazole and MMF. Use omeprazole with caution in transplant patients receiving MMF [see CLINICAL PHARMACOLOGY (12.3)].

7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time.

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 omeprazole.

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. Dose adjustment of omeprazole is not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered. When voriconazole (400 mg Q12h x 1 day, then 200 mg x 6 days) was given with omeprazole (40 mg once daily x 7 days) to healthy subjects, it significantly increased the steady-state C_{max} and AUC₀₋₂₄ of omeprazole, an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4) respectively as compared to when omeprazole was given without voriconazole.

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydro-cilostazol, which has 4 to 7 times the activity of cilostazol, were increased by 29% and 69% respectively. Co-administration of cilostazol with omeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Drugs known to induce CYP2C19 or CYP3A4 (such as rifampin) may lead to decreased omeprazole serum levels. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days), an inducer of CYP3A4, decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C_{max} and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with omeprazole.

Clopidogrel

Omeprazole is an inhibitor of CYP2C19 enzyme. Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of omeprazole 80 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of omeprazole with clopidogrel. When using omeprazole, consider use of alternative anti-platelet therapy [see PHARMACOKINETICS (12.3)].

There are no adequate combination studies of a lower dose of omeprazole or a higher dose of clopidogrel in comparison with the approved dose of clopidogrel.

7.4 Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

7.5 Interactions with Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors [see WARNINGS AND PRECAUTIONS (5.10) and CLINICAL PHARMACOLOGY (12)].

7.6 Combination Therapy with Clarithromycin

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see WARNINGS AND PRECAUTIONS in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs [see CONTRAINDICATIONS in prescribing information for clarithromycin].

7.7 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [see WARNINGS AND PRECAUTIONS (5.11)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with omeprazole in pregnant women. Available

epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use.

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg (based on a body surface area basis for a 60 kg person). However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg (see Animal Data). Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H₂-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837, 317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H₂-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H₂-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) 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 (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) 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 at 13.8 to 138.0 mg/kg/day (about 3.4 to 34 times an oral human doses of 40 mg on a body surface area basis).

Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg /kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.3 Nursing Mothers

Omeprazole is present in human milk. Omeprazole concentrations were measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Caution should be exercised when omeprazole is administered to a nursing woman.

8.4 Pediatric Use

Use of omeprazole in pediatric and adolescent patients 2 to 16 years of age for the treatment of GERD and maintenance of healing of erosive esophagitis is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of omeprazole for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients [SEE CLINICAL PHARMACOLOGY, PHARMACOKINETICS, PEDIATRIC for pharmacokinetic information (12.3) and DOSAGE AND ADMINISTRATION (2), ADVERSE REACTIONS (6.1) and CLINICAL STUDIES (14.6)]. The safety and effectiveness of omeprazole for the treatment of GERD in patients <1 year of age have not been established. The safety and effectiveness of omeprazole for other pediatric uses have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in

death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth [see NONCLINICAL TOXICOLOGY (13.2)].

8.5 Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. 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 (12.3)].

8.6 Hepatic Impairment

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis [see CLINICAL PHARMACOLOGY (12.3)].

8.7 Renal Impairment

No dosage reduction is necessary [SEE CLINICAL PHARMACOLOGY (12.3)].

8.8 Asian Population

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis [see CLINICAL PHARMACOLOGY (12.3)].

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 omeprazole 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.

11 DESCRIPTION

The active ingredient in omeprazole delayed-release capsules is a substituted benzimidazole, 5-methoxy-2-[[[4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is C₁₇H₁₉N₃O₃S, with a molecular weight of 345.42. The structural formula is:

[chemical-structure]

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.

Omeprazole Delayed-Release Capsules meet USP Dissolution Test 2.

Omeprazole 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: magnesium hydroxide, mannitol, methacrylic acid copolymer dispersion, povidone and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, red iron oxide and titanium dioxide. The capsule imprinting ink contains ammonium hydroxide, black iron oxide, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, potassium hydroxide, propylene glycol and shellac.

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 to 6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Table 1 Range of Mean Values from Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing

	Omeprazole 20 mg	Omeprazole 40 mg		
Parameter	Max	Min	Max	Min

*

Single Studies

% Decrease in Basal Acid Output

78*

58 to 80

94

80 to 93

% Decrease in Peak Acid Output

79

50 to 59

88

62 to 68

% Decrease in 24-hr. Intra-gastric Acidity

80 to 97

92 to 94

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.

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.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop omeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Enterochromaffin-like (ECL) Cell Effects

Human gastric biopsy specimens have been obtained from more than 3000 patients (both children and adults) 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 intra-gastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intra-gastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intra-gastric 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 omeprazole 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

Omeprazole 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 to 40% at doses of 20 to 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 to 600 mL/min.

The bioavailability of omeprazole increases slightly upon repeated administration of omeprazole delayed-release capsules.

Omeprazole delayed-release capsule 40 mg was bioequivalent when administered with and without applesauce. However, omeprazole 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 omeprazole 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}, 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.

Table 2 Clarithromycin Tissue Concentrations 2 hours after Dose 1
Tissue Clarithromycin Clarithromycin + Omeprazole

Antrum

10.48 ± 2.01 (n = 5)

19.96 ± 4.71 (n = 5)

Fundus

20.81 ± 7.64 (n = 5)

24.25 ± 6.37 (n = 5)

Mucus

4.15 ± 7.74 (n = 4)

39.29 ± 32.79 (n = 4)

1Mean ± SD (mcg/g)

Concomitant Use with Clopidogrel

In a crossover clinical study, 72 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with omeprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together.

Results from another crossover study in healthy subjects showed a similar pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole 80 mg daily when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 41% to 46% over this time period.

In another study, 72 healthy subjects were given the same doses of clopidogrel and 80 mg omeprazole but the drugs were administered 12 hours apart; the results were similar, indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction.

Concomitant Use with Mycophenolate Mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1,000 mg dose of MMF approximately one hour after the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the C_{max} and 23% reduction in the AUC of MPA.

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:

Table 3 Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared with Adults

Single or Repeated Oral Dosing/ Parameter

Children†

≤20 kg

2 to 5 years

10 mg Children†

> 20 kg

6 to 16 years

20 mg Adults‡

(mean 76 kg)

23 to 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 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 to 1 hour. Plasma clearance averaged 70 mL/min, compared with a value of 500 to 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 mcg/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 mcg/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 mcg/mL by Etest®.

Table 4 Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes^a

Clarithromycin Pretreatment Results Clarithromycin Post-treatment Results

H. pylorinegative – eradicated H. pylori positive – not eradicated

Post-treatment susceptibility results

S^b I^b R^b No MIC

Dual Therapy – (omeprazole 40 mg once daily/clarithromycin 500 three times daily for 14 days followed by omeprazole 20 mg once daily for another 14 days) (Studies 4, 5)

Susceptible^b 108 72 1 26 9

Intermediate^b 1 1

Resistant^b 4 4

Triple Therapy – (omeprazole 20 mg twice daily/clarithromycin 500 mg twice daily/amoxicillin 1 g twice daily for 10 days – Studies 1, 2, 3; followed by omeprazole 20 mg once daily for another 18 days – Studies 1, 2)

Susceptible^b 171 153 7 3 8

Intermediate^b

Resistant^b 14 4 1 6 3

a Includes only patients with pretreatment clarithromycin susceptibility test results

b Susceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 to 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/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 mcg/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*

For susceptibility testing information about *Helicobacter pylori*, see Microbiology section in prescribing information for clarithromycin and amoxicillin.

Effects on Gastrointestinal Microbial Ecology

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also *Clostridium difficile*.

13 NONCLINICAL TOXICOLOGY

13.1 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 (about 0.4 to 34 times a human dose of 40 mg/day, as expressed on a body surface area basis) 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 (about 3.4 times a human dose of 40 mg/day, based on body surface area) for one year, and 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. Gastric adenocarcinoma 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. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.9 times the human dose of 40 mg/day, based on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 34 times the human dose of 40 mg/day on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an in vitro human lymphocyte chromosomal aberration assay, in one of two in vivo mouse micronucleus tests, and in an in vivo bone marrow cell chromosomal aberration assay. Omeprazole was negative in the in vitro Ames test, an in vitro mouse lymphoma cell forward mutation assay, and an in vivo rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times an oral human dose of 40 mg on a body surface area basis) was found to have no effect on fertility and reproductive performance.

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 WARNINGS AND PRECAUTIONS (5)]. 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.

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproductive Toxicology Studies

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times the human dose of 40 mg/day on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 34 times the human dose on a body surface area basis) 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 (about 3.4 to 34 times the human dose of 40 mg/day on a body surface area basis) 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 at 13.8 to 138.0 mg/kg/day (about 3.4 to 34 times the human dose of 40 mg/day on a body surface area basis) [see PREGNANCY, ANIMAL DATA (8.1)].

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 68 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

14.1 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 omeprazole 20 mg once daily than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer % of Patients Healed

Omeprazole Placebo

20 mg a.m.

(n = 99) a.m.

(n = 48)

*

($p \leq 0.01$)

Week 2

*41

13

Week 4

75

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole 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 omeprazole 20 mg once daily than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer % of Patients Healed

Omeprazole Ranitidine

20 mg a.m. 150 mg twice daily

(n = 145) (n = 148)

*

($p < 0.01$)

Week 2

42

34

Week 4

*82

63

Healing occurred significantly faster in patients treated with omeprazole 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 omeprazole were compared with 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer % of Patients Healed

Omeprazole Ranitidine

20 mg

(n = 34) 40 mg

(n = 36) 150 mg twice daily

(n = 35)

*

($p \leq 0.01$)

Week 2

*83

83

53

Week 4

97

100

82

Week 8

100

100

94

H. pylori Eradication in Patients with Duodenal Ulcer Disease

Triple Therapy (omeprazole/clarithromycin/amoxicillin)

Three U.S., randomized, double-blind clinical studies in patients with H. pylori infection and duodenal ulcer disease (n = 558) compared omeprazole plus clarithromycin plus amoxicillin with clarithromycin plus amoxicillin. Two studies (1 and 2) were conducted in patients with an active duodenal ulcer, and the other study (3) 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 omeprazole 20 mg twice daily plus clarithromycin 500 mg twice daily plus amoxicillin 1 g twice daily for 10 days; or clarithromycin 500 mg twice daily plus amoxicillin 1 g twice daily for 10 days. In studies 1 and 2, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg once daily. Endpoints studied were eradication of H. pylori and duodenal ulcer healing (studies 1 and 2 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.

Table 5 Per-Protocol and Intent-to-Treat H. pylori Eradication Rates % of Patients Cured [95% Confidence Interval]

Omeprazole + Clarithromycin + Amoxicillin Clarithromycin + Amoxicillin

Per-Protocol† Intent-to-Treat‡ Per-Protocol† Intent-to-Treat‡

Study 1 * 77 [64, 86]

(n = 64) *69 [57, 79]

(n = 80) 43 [31, 56]

(n = 67) 37 [27, 48]

(n = 84)

Study 2 *78 [67, 88]

(n = 65) *73 [61, 82]

(n = 77) 41 [29, 54]

(n = 68) 36 [26, 47]

(n = 83)

Study 3 *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 1 and 2; history of ulcer within 5 years, study 3) 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 (omeprazole/clarithromycin)

Four randomized, double-blind, multi-center studies (4, 5, 6, and 7) evaluated omeprazole 40 mg once daily plus clarithromycin 500 mg three times daily for 14 days, followed by omeprazole 20 mg once daily, (Studies 4, 5, and 7) or by omeprazole 40 mg once daily (Study 6) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies 4 and 5 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 4 and 228 patients in Study 5. These studies compared the combination regimen to omeprazole and clarithromycin monotherapies. Studies 6 and 7 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in Study 6 and 208 patients in Study 7. These studies compared the combination regimen with 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*.

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

Omeprazole + Clarithromycin Omeprazole Clarithromycin

U.S. Studies

Study 4 74 [60, 85] †‡
(n = 53) 0 [0, 7]
(n = 54) 31 [18, 47]
(n = 42)

Study 5 64 [51, 76] †‡
(n = 61) 0 [0, 6]
(n = 59) 39 [24, 55]
(n = 44)

Non U.S. Studies

Study 6 83 [71, 92] ‡
(n = 60) 1 [0, 7]
(n = 74) N/A
Study 7 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 with omeprazole therapy alone.

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

Table 7 Duodenal Ulcer Recurrence Rates by *H. pylori* Eradication Status % of Patients with Ulcer Recurrence

H. pylori eradicated# *H. pylori* not eradicated#

U.S. Studies†

6 months post-treatment

Study 4 *35

(n = 49) 60

(n = 88)

Study 5 *8

(n = 53) 60

(n = 106)

Non U.S. Studies‡

6 months post-treatment

Study 6 *5

(n = 43) 46

(n = 78)

Study 7 *6

(n = 53) 43

(n = 107)

12 months post-treatment

Study 6 *5

(n = 39) 68

(n = 71)

H. pylori eradication status assessed at same time point as ulcer recurrence

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

‡ Combined results for omeprazole + clarithromycin and omeprazole treatment arms

*($p \leq 0.01$) versus proportion with duodenal ulcer recurrence who were not H. pylori eradicated

14.2 Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once daily, 20 mg once daily, 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)

Omeprazole

20 mg once daily

(n = 202) Omeprazole

40 mg once daily

(n = 214) Placebo

(n = 104)

Week 4 47.5 ** 55.6 ** 30.8

Week 8 74.8 ** 82.7 **, + 48.1

**($p < 0.01$) omeprazole 40 mg or 20 mg versus placebo

+($p < 0.05$) omeprazole 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 daily, 20 mg once daily, and ranitidine 150 mg twice a day were evaluated.

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

Omeprazole

20 mg once daily

(n = 200) Omeprazole

40 mg once daily

(n = 187) Ranitidine

150 mg twice daily.

(n = 199)

Week 4 63.5 78.1 **,++ 56.3

Week 8 81.5 91.4 **,++ 78.4

** (p < 0.01) omeprazole 40 mg versus ranitidine

++ (p < 0.01) omeprazole 40 mg versus 20 mg

14.3 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^a

Omeprazole

20 mg a.m. Omeprazole

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)

^a Defined as complete resolution of heartburn

* (p < 0.005) versus 10 mg

† (p < 0.005) versus placebo

14.4 Erosive Esophagitis

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of omeprazole 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 Omeprazole

(n = 83)

40 mg Omeprazole

(n = 87)

Placebo

(n = 43)

4

39**

45**

7

8

74**

75**

14

** (p < 0.01) omeprazole versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole is effective in severe GERD. In comparisons with histamine H₂-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole 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 omeprazole 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 Of Healing of Erosive Esophagitis

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

Life Table Analysis

Omeprazole

20 mg once daily

(n = 138) Omeprazole

20 mg 3 days per week

(n = 137)

Placebo

(n = 131)

Percent in endoscopic remission at 6 months * 70 34 11

*(p < 0.01) Omeprazole 20 mg once daily versus Omeprazole 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, omeprazole 20 mg daily and 10 mg daily were compared with 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

Omeprazole

20 mg once daily

(n = 131) Omeprazole

10 mg once daily

(n = 133) Ranitidine

150 mg twice daily

(n = 128)

Percent in endoscopic remission at 12 months * 77 ‡ 58 46

*(p = 0.01) omeprazole 20 mg once daily versus omeprazole 10 mg once daily or Ranitidine.

‡ (p = 0.03) omeprazole 10 mg once daily versus Ranitidine.

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

14.5 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, omeprazole 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 (2)]. Omeprazole 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 omeprazole. 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 omeprazole developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of omeprazole [see ADVERSE REACTIONS (6)].

14.6 Pediatric GERD

Symptomatic GERD

The effectiveness of omeprazole for the treatment of nonerosive GERD in pediatric patients 2 to 16 years of age is based in part on data obtained from pediatric patients in an uncontrolled Phase III studies [see USE IN SPECIFIC POPULATIONS (8.4)].

The study enrolled 113 pediatric patients 2 to 16 years of age with a history of symptoms suggestive of nonerosive GERD. Patients were administered a single dose of omeprazole (10 mg or 20 mg, based on body weight) for 4 weeks either as an intact capsule or as an open capsule in applesauce. Successful response was defined as no moderate or severe episodes of either pain-related symptoms or vomiting/regurgitation during the last 4 days of treatment. Results showed success rates of 60% (9/15; 10 mg omeprazole) and 59% (58/98; 20 mg omeprazole), respectively.

Healing of Erosive Esophagitis

In an uncontrolled, open-label dose-titration study, healing of erosive esophagitis in pediatric patients 1 to 16 years of age required doses that ranged from 0.7 to 3.5 mg/kg/day (80 mg/day). Doses were initiated at 0.7 mg/kg/day. Doses were increased in increments of 0.7 mg/kg/day (if intraesophageal pH showed a pH of < 4 for less than 6% of a 24-hour study). After titration, patients remained on treatment for 3 months. Forty-four percent of the patients were healed on a dose of 0.7 mg/kg body weight; most of the remaining patients were healed with 1.4 mg/kg after an additional 3 months' treatment. Erosive esophagitis was healed in 51 of 57 (90%) children who completed the first course of treatment in the healing phase of the study. In addition, after 3 months of treatment, 33% of the children had no overall symptoms, 57% had mild reflux symptoms, and 40% had less frequent regurgitation/vomiting.

Maintenance of Healing of Erosive Esophagitis

In an uncontrolled, open-label study of maintenance of healing of erosive esophagitis in 46 pediatric patients, 54% of patients required half the healing dose. The remaining patients increased the healing dose (0.7 to a maximum of 2.8 mg/kg/day) either for the entire maintenance period, or returned to half the dose before completion. Of the 46 patients who entered the maintenance phase, 19 (41%) had no relapse. In addition, maintenance therapy in erosive esophagitis patients resulted in 63% of patients

having no overall symptoms.

15 REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol, 20, No. 2, NCCLS, Wayne, PA, January 2000.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omeprazole delayed-release capsules, USP 10 mg are available for oral administration as hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. “APO 010” is imprinted on each capsule in black ink. They are supplied as follows:

Bottles of 30 (NDC 60505-0145-0)
Bottles of 100 (NDC 60505-0145-2)
Bottles of 1,000 (NDC 60505-0145-1)
Blisters of 70 (NDC 60505-0145-3)
Blisters of 100 (NDC 60505-0145-7)

Omeprazole delayed-release capsules, USP 20 mg are available for oral administration as hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. “APO 020” is imprinted on each capsule in black ink. They are supplied as follows:

Bottles of 30 (NDC 60505-0065-0)
Bottles of 100 (NDC 60505-0065-2)
Bottles of 500 (NDC 60505-0065-5)
Bottles of 1,000 (NDC 60505-0065-1)
Bottles of 5,000 (NDC 60505-0065-8)
Blisters of 70 (NDC 60505-0065-3)
Blisters of 100 (NDC 60505-0065-7)
Package of 12 Bottles each containing 30 Capsules (NDC 60505-3952-3)

Omeprazole delayed-release capsules, USP 40 mg are available for oral administration as hard gelatin capsules with a pink opaque body and a reddish brown opaque cap. “APO 040” is imprinted on each capsule in black ink. They are supplied as follows:

Bottles of 30 (NDC 60505-0146-0)
Bottles of 90 (NDC 60505-0146-9)
Bottles of 100 (NDC 60505-0146-2)
Bottles of 500 (NDC 60505-0146-1)

Storage

Store omeprazole delayed-release capsules in a tight container protected from light and moisture.

Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

“See FDA-Approved Medication Guide”

Omeprazole delayed-release capsule should be taken before eating. Patients should be informed that the omeprazole delayed-release capsule should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of an omeprazole 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.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [see WARNINGS AND PRECAUTIONS (5.5)].

Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [see WARNINGS AND PRECAUTIONS (5.8)].

APOTEX INC.
OMEPRAZOLE DELAYED-RELEASE CAPSULES, USP
10 mg, 20 mg and 40 mg

Manufactured by Manufactured for
Apotex Inc. Apotex Corp.
Toronto, Ontario Weston, Florida
Canada M9L 1T9 USA 33326

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Revision: 19

MEDICATION GUIDE

MEDICATION GUIDE

Omeprazole Delayed-Release Capsules, USP

(oh mep' ra zole)

Read this Medication Guide before you start taking omeprazole delayed-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about omeprazole delayed-release capsules?

Omeprazole delayed-release capsules may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

Omeprazole delayed-release capsules can cause serious side effects, including:

Diarrhea. Omeprazole may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection (*Clostridium difficile*) in your intestines.

Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.

Bone fractures. People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take omeprazole delayed-release capsules exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take omeprazole delayed-release capsules.

Omeprazole can have other serious side effects. See “What are the possible side effects of omeprazole delayed-release capsules?”

What are omeprazole delayed-release capsules?

Omeprazole delayed-release capsules is a prescription medicine called a proton pump inhibitor (PPI).

Omeprazole delayed-release capsules reduces the amount of acid in your stomach. Omeprazole delayed-release capsules are used in adults:

for up to 8 weeks for the healing of duodenal ulcers. The duodenal area is the area where food passes when it leaves the stomach.

with certain antibiotics to treat an infection caused by bacteria called *H. pylori*. Sometimes *H. pylori* bacteria can cause duodenal ulcers. The infection needs to be treated to prevent the ulcers from coming back.

for up to 8 weeks for healing stomach ulcers.

for up to 4 weeks to treat heartburn and other symptoms that happen with gastroesophageal reflux disease (GERD).

GERD happens when acid in your stomach backs up into the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste, or burping.

for up to 8 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE). If needed, your doctor may decide to prescribe another 4 weeks of omeprazole delayed-release capsules.

to maintain healing of the esophagus. It is not known if omeprazole delayed-release capsules is safe and effective when used for longer than 12 months (1 year) for this purpose.

for the long-term treatment of conditions where your stomach makes too much acid. This includes a rare condition called Zollinger-Ellison Syndrome.

For children and adolescents 2 to 17 years of age, omeprazole delayed-release capsules are used:

for up to 4 weeks to treat heartburn and other symptoms that happen with gastroesophageal reflux disease (GERD).

for up to 8 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE)

to maintain healing of the esophagus. It is not known if omeprazole delayed-release capsules are safe and effective when used longer than 12 months (1 year) for this purpose.

It is not known if omeprazole delayed-release capsules are safe and effective for the treatment of gastroesophageal reflux disease (GERD) in children under 1 year of age.

Who should not take omeprazole delayed-release capsules?

Do not take omeprazole delayed-release capsules if you:

are allergic to omeprazole delayed-release capsules or any of the ingredients in omeprazole delayed-release capsules. See the end of this Medication Guide for a complete list of ingredients in omeprazole delayed-release capsules.

are allergic to any other Proton Pump Inhibitor (PPI) medicine.

What should I tell my doctor before taking omeprazole delayed-release capsules?

Before you take omeprazole delayed-release capsules, tell your doctor if you:

have been told that you have low magnesium levels in your blood

have liver problems

have any other medical conditions

are pregnant or plan to become pregnant. It is not known if omeprazole will harm your unborn baby.

are breastfeeding or plan to breastfeed. Omeprazole passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take omeprazole delayed-release capsules.

Tell your doctor about all of the medicines you take including prescription and non-prescription drugs, anti-cancer drugs, vitamins and herbal supplements. Omeprazole delayed-release capsules may affect how other medicines work, and other medicines may affect how omeprazole delayed-release capsules works.

Especially tell your doctor if you take:

atazanavir (Reyataz)
nelfinavir (Viracept)
saquinavir (Fortovase)
cilostazol (Pletal)
ketoconazole (Nizoral)
voriconazole (Vfend)
an antibiotic that contains ampicillin, amoxicillin or clarithromycin
products that contain iron
warfarin (Coumadin, Jantoven)
digoxin (Lanoxin)
tacrolimus (Prograf)
diazepam (Valium)
phenytoin (Dilantin)
disulfiram (Antabuse)
clopidogrel (Plavix)
St. John's Wort (Hypericum perforatum)
rifampin (Rimactane, Rifater, Rifamate),
erlotinib (Tarceva)
methotrexate
mycophenolate mofetil (Cellcept)

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines that you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take omeprazole delayed-release capsules?

Take omeprazole delayed-release capsules exactly as prescribed by your doctor.

Do not change your dose or stop omeprazole delayed-release capsules without talking to your doctor.

Take omeprazole delayed-release capsules at least 1 hour before a meal.

Swallow omeprazole delayed-release capsules whole. Do not chew or crush omeprazole delayed-release capsules.

If you have trouble swallowing omeprazole delayed-release capsules, you may take as follows:

Place 1 tablespoon of applesauce into a clean bowl.

Carefully open the capsule and empty the contents (pellets) onto the applesauce. Mix the pellets with the applesauce.

Swallow the applesauce and pellet mixture right away with a glass of cool water. Do not chew or crush the pellets. Do not store the applesauce and pellet mixture for later use.

If you forget to take a dose of omeprazole delayed-release capsules, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.

If you take too much omeprazole delayed release capsules, tell your doctor right away.

What are the possible side effects of omeprazole delayed-release capsules?

Omeprazole can cause serious side effects, including:

See "What is the most important information I should know about omeprazole?"

Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis). Using omeprazole delayed-release capsules for a long period of time may increase the risk of inflammation to your stomach lining. You may or may not have symptoms. Tell your doctor if you have stomach pain, nausea, vomiting, or weight loss.

Vitamin B-12 deficiency. Omeprazole delayed-release capsules reduces the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor about the

possibility of vitamin B-12 deficiency if you have been on omeprazole delayed-release capsules for a long time (more than 3 years).

Low magnesium levels in your body. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

Tell your doctor right away if you develop any of these symptoms:

- seizures
- dizziness
- abnormal or fast heart beat
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking omeprazole delayed-release capsules or during treatment if you will be taking omeprazole delayed-release capsules for a long period of time.

The most common side effects with omeprazole delayed-release capsules in adults and children include:

- headache
- stomach pain
- nausea
- diarrhea
- vomiting
- gas

In addition to the side effects listed above, the most common side effects in children 2 to 16 years of age include:

- respiratory system events
- fever

Other side effects:

Serious allergic reactions. Tell your doctor if you get any of the following symptoms with omeprazole:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop omeprazole if these symptoms happen.

Tell your doctor if you have any side effect that bothers you or that do not go away. These are not all the possible side effects with omeprazole delayed-release capsules.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store omeprazole delayed-release capsules?

Store omeprazole delayed-release capsules at room temperature between 68°F to 77°F (20°C to 25°C). Keep the container of omeprazole delayed-release capsules dry and away from light.

Keep omeprazole delayed-release capsules and all medicines out of the reach of children.

General information about omeprazole delayed-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use omeprazole delayed-release capsules for a condition for which it was not prescribed. Do not give omeprazole delayed-release capsules to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about omeprazole delayed-release capsules.

For more information, ask your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

For more information contact Apotex Corp., Drug Safety at 1-800-706-5575.

Instructions for Use

For instructions on taking omeprazole delayed-release capsules, please see “How should I take omeprazole delayed-release capsules?”

What are the ingredients in omeprazole delayed-release capsules?

Active ingredient in omeprazole delayed-release capsules: omeprazole

Inactive ingredients in omeprazole delayed-release capsules: magnesium hydroxide, mannitol, methacrylic acid copolymer dispersion, povidone and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, red iron oxide and titanium dioxide. The capsule imprinting ink contains ammonium hydroxide, black iron oxide, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, potassium hydroxide, propylene glycol and shellac.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.

APOTEX INC.

OMEPRAZOLE DELAYED-RELEASE CAPSULES, USP

10 mg, 20 mg and 40 mg

Manufactured by Manufactured for
Apotex Inc. Apotex Corp.
Toronto, Ontario Weston, Florida
Canada M9L 1T9 USA 33326

January 2015

PRINCIPAL DISPLAY PANEL

Rx Only
NDC: 67296-0897-1
LEVOFLOXACIN
500MG
7 Tablets
Lot: 12014A 1 Exp: 08/14

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)

Mfg. by: Aurobindo Pharma Limited
Mahaboob Nagar AP-509302, India
65862-537-50
Dist. by: Redpharm Drug Eden Prairie, MN 55344

LCN: 363988



4
08971
3
67296

Rx Only
NDC: 67296-0897-2
LEVOFLOXACIN
500MG
10 Tablets
Lot: 13005A 1 Exp: 02/15

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)

Mfg. by: Aurobindo Pharma Limited
Mahaboob Nagar AP-509302, India
65862-537-50
Dist. by: Redpharm Drug Eden Prairie, MN 55344

LCN: 500006



1
08972
3
67296

Rx Only
NDC: 67296-0897-5
LEVOFLOXACIN
500MG
5 Tablets
Lot: 13025A 1 Exp: 09/15

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)

Mfg. by: Aurobindo Pharma Limited
Mahaboob Nagar AP-509302, India
65862-537-50
Dist. by: Redpharm Drug Eden Prairie, MN 55344

LCN: 543404



2
08975
3
67296

OMEPRAZOLE

omeprazole capsule, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67296-0882(NDC:60505-0065)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OMEPRAZOLE (UNII: KG60484QX9) (OMEPRAZOLE - UNII:KG60484QX9)	OMEPRAZOLE	20 mg

Inactive Ingredients

Ingredient Name	Strength
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
MAGNESIUM HYDROXIDE (UNII: NBZ3QY004S)	
MANNITOL (UNII: 3OWL53L36A)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
ALCOHOL (UNII: 3K9958V90M)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
POVIDONE K30 (UNII: U725QWY32X)	

Product Characteristics

Color	pink (opaque) , brown (reddish brown)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	APO;020
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67296-0882-1	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/11/2003	
2	NDC:67296-0882-2	20 in 1 BOTTLE; Type 0: Not a Combination Product	11/11/2003	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076048	11/11/2003	

Labeler - RedPharm Drug, Inc. (828374897)

Establishment

Name	Address	ID/FEI	Business Operations
RedPharm Drug, Inc.		828374897	repack(67296-0882) , relabel(67296-0882)

Revised: 1/2020

RedPharm Drug, Inc.