OMEPRAZOLE- omeprazole capsule, delayed release
Mas Management Group, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OMEPRAZOLE DELAYED-RELEASE CAPSULES safely and effectively. See full prescribing information for OMEPRAZOLE DELAYED-RELEASE CAPSULES.

OMEPRAZOLE Delayed-Release Capsules, for oral use
Initial U.S. Approval: 1989

RECENT MAJOR CHANGES

Contraindications (4) 02/2016
Warnings and Precautions, Atrophic Gastritis (5.2) removed 10/2016

Warnings and Precautions, Cutaneous and Systemic Lupus Erythematosus (5.5) 10/2016

INDICATIONS AND USAGE

Omeprazole delayed-release capsules are a proton pump inhibitor (PPI) indicated for the: (1)

- Treatment of active duodenal ulcer in adults (1.1)
- Eradication of Helicobacter pylori to reduce the risk of duodenal ulcer recurrence in adults (1.2)
- Treatment of active benign gastric ulcer in adults (1.3)
- Treatment of symptomatic gastroesophageal reflux disease (GERD) in patients 2 years of age and older (1.4)
- Maintenance of healing of EE due to acid-mediated GERD in patients 2 years of age and older (1.6)
- Pathologic hypersecretory conditions in adults (1.7)

DOSAGE FORMS AND STRENGTHS

- Omeprazole delayed-release capsules: 10 mg, 20 mg, and 40 mg. (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation. (4)
- Patients receiving rilpivirine-containing products. (4, 7)
- Refer to the Contraindications section of the prescribing information for clarithromycin and amoxicillin, when administered in combination with omeprazole. (4)

WARNINGS AND PRECAUTIONS

- Gastric Malignancy: In adults, symptomatic response does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue omeprazole and refer to specialist for evaluation. (5.5)
- Interaction with Clopidogrel: Avoid concomitant use of omeprazole.(5.6, 7)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.8)
- Interaction with St. John’s Wort or Rifampin: Avoid concomitant use of omeprazole. (5.9, 7)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased Chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop omeprazole at least 14 days before assessing CgA levels. (5.10, 7)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of omeprazole. (5.11, 7).

ADVERSE REACTIONS

(5)
Adults: Most common adverse reactions in adults (incidence ≥ 2%) are (5)

- Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence. (6)

Pediatric patients (2 to 16 years of age): (5)
- Safety profile similar to that in adults, except that respiratory system events and fever were the most frequently reported reactions in pediatric studies. (8.4)

To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1-888-721-7115 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (5)

---------- **DRUG INTERACTIONS** ----------

See full prescribing information for a list of clinically important drug interactions. (7) (6)
(6)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. (6)
(6)
Revised: 12/2016 (6)
See 17 for Medication Guide.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Omeprazole delayed-release capsules are a proton pump inhibitor (PPI) indicated for the:

- Treatment of active duodenal ulcer in adults (1.1)
- Eradication of Helicobacter pylori to reduce the risk of duodenal ulcer recurrence in adults (1.2)
- Treatment of active benign gastric ulcer in adults (1.3)
- Treatment of symptomatic gastroesophageal reflux disease (GERD) in patients 2 years of age and older (1.4)
- Maintenance of healing of EE due to acid-mediated GERD in patients 2 years of age and older (1.6)
- Pathologic hypersecretory conditions in adults (1.7)

1.1 Treatment of Active Duodenal Ulcer

Omeprazole delayed-release capsules 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.

1.2 Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Triple Therapy

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

Dual Therapy

Omeprazole delayed-release capsules in combination with clarithromycin are indicated for treatment of patients with H. pylori infection and duodenal ulcer disease to eradicate H. pylori in adults.

Among patients who fail therapy, omeprazole delayed-release capsules with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted [see Clinical Pharmacology (12.4) and the clarithromycin prescribing information, Microbiology sectio n].

1.3 Treatment of Active Benign Gastric Ulcer

Omeprazole delayed-release capsules are indicated for short-term treatment (4 to 8 weeks) of active benign gastric ulcer in adults.

1.4 Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)

Omeprazole delayed-release capsules are indicated for the treatment of heartburn and other symptoms associated with GERD for up to 4 weeks in patients 2 years of age and older.

1.5 Treatment of Erosive Esophagitis (EE) Due to Acid-Mediated GERD

Pediatric Patients 2 Years of Age to Adults

Omeprazole delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) of EE due to acid-mediated GERD that has been diagnosed by endoscopy in patients 2 years of age and older.

The efficacy of omeprazole delayed-release capsules used for longer than 8 weeks in patients with EE 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 EE or GERD symptoms (e.g., heartburn), additional 4 to 8 week courses of omeprazole delayed-release capsules may be considered.

1.6 Maintenance of Healing of EE Due to Acid-Mediated GERD

Omeprazole delayed-release capsules are indicated for the maintenance healing of EE due to acid-mediated GERD in patients 2 years of age and older.

Controlled studies do not extend beyond 12 months.

1.7 Pathological Hypersecretory Conditions

Omeprazole delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis) in adults.

3 DOSAGE FORMS AND STRENGTHS

Omeprazole delayed-release capsules USP, 10 mg, are size ‘3’ two piece hard gelatin capsule with

light blue to blue body with “G” imprinting in black ink and orange cap with “G230” imprinting in black ink. The capsules are filled with white to off-white pellets.

Omeprazole delayed-release capsules USP, 20 mg, are size ‘2’ two piece hard gelatin capsule with light blue to blue body with “G” imprinting in black ink and light blue to blue cap with “G231” imprinting in black ink. The capsules are filled with white to off-white pellets.

Omeprazole delayed-release capsules USP, 40 mg, are size ‘1’ two piece hard gelatin capsule with orange body with ‘G’ imprinting in black ink and light blue to blue cap with ‘G232’ imprinting in black ink. The capsules are filled with white to off-white pellets.

4 CONTRAINDICATIONS

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- Omeprazole is 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, interstitial nephritis, and urticaria [see Warnings and Precautions (5.2), Adverse Reactions (6)].
- Proton pump inhibitors (PPIs), including omeprazole, are contraindicated in patients receiving rilpivirine-containing products [see Drug Interactions (7)].
- 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 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

5.2 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)].

5.3 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 the corresponding prescribing information.

5.4 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 (2.1), Adverse Reactions (6.3)].

5.5 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving omeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

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) and Clinical Pharmacology (12.3)].

5.7 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 in patients treated with omeprazole.

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 Interaction 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)]. 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 [see Drug Interactions (7)].

5.11 Interaction with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) 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)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Interstitial Nephritis [see Warnings and Precautions (5.2)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.3)]
- Bone Fracture [see Warnings and Precautions (5.4)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.5)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.7)]
- Hypomagnesemia [see Warnings and Precautions (5.8)]

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 ≥ 2%) from omeprazole-treated patients enrolled in these studies included headache (7%), abdominal pain (5%), nausea (4%), diarrhea (4%), vomiting (3%), and flatulence (3%).

Additional adverse reactions that were reported with an incidence ≥1% included acid regurgitation (2%), upper respiratory infection (2%), constipation (2%), dizziness (2%), rash (2%), asthenia (1%), back pain (1%), and cough (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 frequently reported in the 2 to 16 year age group (19%). In addition, accidental injuries were frequently reported in the 2 to 16 year age group (4%) [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 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of omeprazole. 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; systemic lupus erythematosus

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, cutaneous lupus erythematosus 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, leukocytosis

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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. Reproduction studies in rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 3.4 to 34 times an oral human dose of 40 mg (based on a body surface area for a 60 kg person).

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole (an enantiomer of omeprazole) magnesium in rats and rabbits during organogenesis with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg esomeprazole or 40 mg omeprazole (based on body surface area for a 60 kg person). 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 esomeprazole or 40 mg omeprazole. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age [see Data].

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

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% with 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

Omeprazole

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 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis 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) administered during organogenesis 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 mg/kg/day (about 3.4 to 34 times an oral human doses of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

Esomeprazole

The data described below was generated from studies using esomeprazole, an enantiomer of omeprazole. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 40 mg esomeprazole or 40 mg omeprazole.

No effects on embryo-fetal development were observed in reproduction studies 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) or in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis) administered during organogenesis.

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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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.

A follow up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal day 2 to adulthood was performed with esomeprazole magnesium at oral doses of 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) where esomeprazole administration was from either gestational day 7 or gestational day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

8.2 Lactation

Risk Summary

Limited data suggest omeprazole may be present in human milk. There are no clinical data on the effects of omeprazole on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for omeprazole and any potential adverse effects on the breastfed infant from omeprazole or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of omeprazole have been established in pediatric patients 2 to 16 years for the treatment of symptomatic GERD, treatment of EE due to acid-mediated GERD, and maintenance of healing of EE due to acid-mediated GERD. Use of omeprazole in this age group is supported by adequate and well-controlled studies in adults and uncontrolled safety, efficacy and pharmacokinetic studies performed in pediatric and adolescent patients [see Clinical Pharmacology (12.3), Clinical Studies (14.8)].

In the pediatric population, adverse reactions of the respiratory system were frequently reported in the entire (2 to 16 year) age group. Accidental injuries were frequently reported in the 2 to 16 year age group [see Adverse Reactions (6.1)].

The safety and effectiveness of omeprazole delayed-release capsules have not been established in:

- patients less than 1 year of age for:
- Treatment of symptomatic GERD
- Maintenance of healing of EE due to acid-mediated GERD
- pediatric patients for:
- Treatment of active duodenal ulcer
- H.pylori eradication to reduce the risk of duodenal ulcer recurrence
- Treatment of active benign gastric ulcer
- Pathological hypersecretory conditions
- patients less than 1 month of age for any indication.

Juvenile Animal Data

Esomeprazole, an enantiomer of omeprazole, was shown to decrease body weight, body weight gain, femur weight, femur length, and overall growth at oral doses about 34 to 68 times a daily human dose of 40 mg esomeprazole or 40 mg omeprazole based on body surface area in a juvenile rat toxicity study. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 40 mg esomeprazole or 40 mg omeprazole.

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 esomeprazole or 40 mg omeprazole 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 esomeprazole or 40 mg omeprazole 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.

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

In patients with hepatic impairment (Child-Pugh Class A, B, or C) exposure to omeprazole substantially increased compared to healthy subjects. Dosage reduction of omeprazole to 10 mg once daily is recommended for patients with hepatic impairment for maintenance of healing of EE [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

8.7 Asian Population

In studies of healthy subjects, Asians had approximately a four-fold higher exposure than Caucasians. Dosage reduction of omeprazole to 10 mg once daily is recommended for Asian patients for maintenance of healing of EE [see Dosage and Administration (2.1), Clinical Pharmacology (12.5)].

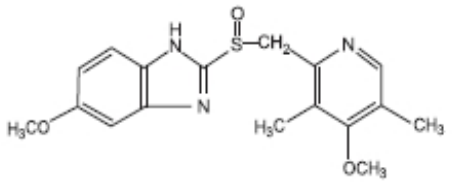
10 OVERDOSAGE

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.

If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

11 DESCRIPTION

The active ingredient in omeprazole delayed-release capsules USP 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 C 17H 19N 3O 3S, with a molecular weight of 345.42. The structural formula is:



Omeprazole USP 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 USP is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole USP in the form of enteric-coated granules with the following inactive ingredients: anhydrous lactose, cetyl alcohol, di-sodium hydrogen phosphate dihydrate, hypromellose, hypromellose phthalate, mannitol, simethicone emulsion 30%, sodium lauryl sulfate and sugar sphere.

The capsule shell for omeprazole delayed-release capsules USP, 10 mg contains FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No.10, gelatin, FD&C Blue No.1, sodium lauryl sulfate and titanium dioxide.

The capsule shell for omeprazole delayed-release capsules USP, 20 mg contains FD&C Blue No.1, gelatin, sodium lauryl sulfate and titanium dioxide.

The capsule shell for omeprazole delayed-release capsules USP, 40 mg contains FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No.10, gelatin, FD&C Blue No.1, sodium lauryl sulfate and titanium dioxide.

The imprinting ink has the following components: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide.

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.

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 healthy subjects 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 5: 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**
% Decrease in Basal Acid Output	78 *	58 - 80	94 [1]	80 - 93
% Decrease in Peak Acid Output	79 [1]	50 - 59	88 [1]	62 - 68
% Decrease in 24-hr. Intragastric Acidity		80 - 97		92 - 94

* Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

12.3 Pharmacokinetics

Omeprazole is a time-dependent inhibitor of CYP2C19, resulting in autoinhibition and nonlinear pharmacokinetics. The systemic exposure increases in a more than dose proportional manner after multiple oral doses of omeprazole. Compared to the first dose, the systemic exposure (C_{max} and AUC_{0-24h}) at steady state following once a day dosing increased by 61% and 62%, respectively, compared to after the first dose for the 20 mg dose of omeprazole delayed-release capsules and increased by 118% and 175%, respectively, for the 40 mg dose of omeprazole delayed-release capsules.

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 concentrations 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.

Based on a relative bioavailability study, the AUC and C_{max} of omeprazole for delayed-release oral suspension were 87% and 88% of those for omeprazole delayed-release capsules, respectively.

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

The systemic exposure (C_{max} and AUC) are similar when a 40 mg omeprazole delayed-release capsule is administered with and without applesauce. However, administration of a 20 mg omeprazole delayed-release capsule with applesauce, results in a mean 25% reduction in C_{max} without a significant change in AUC compared to administration without applesauce. The clinical relevance of this finding is unknown.

Distribution

Protein binding is approximately 95%.

Elimination

Metabolism

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system. The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Excretion

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma concentrations of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Table 6: Clarithromycin Tissue Concentrations 2 hours after Dose [*]

Tissue	Clarithromycin	Clarithromycin + Omeprazole
Antrum	10.48 ± 2.01 (n = 5)	19.96 ± 4.71 (n = 5)
Fundus	20.81 ± 7.64 (n = 5)	24.25 ± 6.37 (n = 5)
Mucus	4.15 ± 7.74 (n = 4)	39.29 ± 32.79 (n = 4)

[*] Mean ± SD (μg/g)

12.5 Pharmacogenomics

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are extensive metabolizers and those carrying two loss of- function alleles are poor metabolizers. In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19.

The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.

In a pharmacokinetic study of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four-fold of that in Caucasians [see Dosage and Administration (2.1), Use in Specific Populations (8.7)].

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 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.

14 CLINICAL STUDIES

14.1 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 20 mg a.m. (n = 99)	Placebo a.m. (n = 48)
Week 2	41 *	13
Week 4	75 *	27

* ($p \leq 0.01$)

14.3 Active Benign 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.

14.5 EE due to Acid-Mediated GERD

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 EE of grade 2 or above, the percentage healing rates (per protocol) were as follows:

	20 mg Omeprazole (n = 83)	40 mg Omeprazole (n = 87)	Placebo (n = 43)
Week 4	39 *	45 *	7
Week 8	74 *	75 *	14

* ($p < 0.01$) omeprazole versus placebo.

14.6 Maintenance of Healing of EE due to Acid-Mediated GERD

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 EE 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

*

14.7 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)].

14.8 Pediatric Studies for the Treatment of Symptomatic GERD, Treatment of EE due to Acid-Mediated GERD, and Maintenance of Healing of EE due to Acid-Mediated GERD

Treatment of Symptomatic GERD

The effectiveness of omeprazole for the treatment of symptomatic GERD in pediatric patients 2 to 16 years of age is based in part on data obtained from pediatric patients in an uncontrolled clinical study.

The study enrolled 113 pediatric patients 2 to 16 years of age with a history of symptoms suggestive of symptomatic 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.

Treatment of EE due to Acid-Mediated GERD

In an uncontrolled, open-label dose-titration study, for the treatment of EE 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. EE 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 EE due to Acid-Mediated GERD

In an uncontrolled, open-label study of maintenance of healing of EE in 46 pediatric patients 1 to 16 years of age, 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 during follow-up (range 4 to 25 months). In addition, maintenance therapy in EE patients resulted in 63% of patients having no overall symptoms.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. CLSI Document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania, 19087, USA 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omeprazole delayed-release capsules USP, 20 mg, are size ‘2’ two piece hard gelatin capsule with light blue to blue body with “G” imprinting in black ink and light blue to blue cap with “G231” imprinting in black ink. The capsules are filled with white to off-white pellets. They are supplied as follows:

NDC 69677-180-30 bottles of 30
NDC 69677-180-60 bottles of 60
NDC 69677-180-90 bottles of 90
NDC 69677-180-01 bottles of 120

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 to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]..

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (*MEDICATION GUIDE* and *INSTRUCTIONS FOR USE*).

Adverse Reactions

Advise patients to report to their healthcare provider if they experience any signs or symptoms consistent with:

- Hypersensitivity reactions [see Contraindications (4)].
- Acute Interstitial Nephritis [see Warnings and Precautions (5.2)].
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.3)].
- Bone Fracture [see Warnings and Precautions (5.4)].
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.5)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.7)].
- Hypomagnesemia [see Warnings and Precautions (5.8)].

Drug Interactions

Advise patients to report to their healthcare provider if they start treatment with clopidogrel, St. John’s Wort or rifampin; or, if they take high-dose methotrexate [see Warnings and Precautions (5.6, 5.9,

5.11)].

Administration

- Take omeprazole delayed-release capsules before meals.
- Antacids may be used concomitantly with omeprazole delayed-release capsules.
- Missed doses: If a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, do not take the missed dose, and take the next dose on time. Do not take two doses at one time to make up for a missed dose.

Omeprazole Delayed-Release Capsules

- Swallow omeprazole delayed-release capsules whole; do not chew.
- For patients unable to swallow an intact capsule, omeprazole delayed-release capsules can be opened and administered in applesauce, as described in the Medication Guide.

Manufactured by:

Glenmark Pharmaceuticals Limited
Colvale-Bardez, Goa 403 513, India

Manufactured for:

Glenmark Pharmaceuticals Inc., USA
Mahwah, NJ 07430

Questions? 1 (888)721-7115
www.glenmarkpharma.com/usa

December 2016

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:

- **A type of kidney problem (acute interstitial nephritis).** Some people who take proton pump inhibitor (PPI) medicines, including omeprazole delayed-release capsules, may develop a kidney problem called acute interstitial nephritis that can happen at any time during treatment with omeprazole delayed-release capsules. Call your doctor if you have a decrease in the amount that you urinate or if you have blood in your urine.
- **Diarrhea.** Omeprazole delayed-release capsules 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 PPI 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.
- **Certain types of lupus erythematosus**. Lupus erythematosus is an autoimmune disorder (the body's immune cells attack other cells or organs in the body). Some people who take proton PPI medicines, including omeprazole delayed-release capsules, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

Omeprazole delayed-release capsules 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 are a prescription medicine called a proton pump inhibitor (PPI). Omeprazole delayed-release capsules reduce 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 for 10 to 14 days to treat an infection caused by bacteria called H. pylori. If needed, your doctor may decide to prescribe another 14 to 18 days of omeprazole delayed-release capsules by itself after the antibiotics. 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 are 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 2 to 16 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 treat gastroesophageal reflux disease (GERD) with acid-related damage to the lining of the esophagus [called erosive esophagitis (or EE) due to acid-mediated GERD].
- 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.

Who should not take omeprazole delayed-release capsules?

Do not take omeprazole delayed-release capsules if you:
- are allergic to omeprazole 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.
- are taking a medicine that contains rilpivirine (EDURANT, COMPLERA) used to treat HIV-1 (Human Immunodeficiency Virus).

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

Before taking omeprazole delayed-release capsules, tell your doctor about all of your medical conditions, including 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 delayed-release capsules 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 over-the-counter medicines, 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 an antibiotic that contains clarithromycin or amoxicillin, or if you take clopidogrel (Plavix), methotrexate (Otrxup, Rasuvo, Trexall), St. John's Wort (Hypericum perforatum), or rifampin (Rimactane, Rifater, Rifamate).

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.
- Omeprazole delayed-release capsules are usually taken 1 time each day. Your doctor will tell you the time of day to take omeprazole delayed-release capsules, based on your medical condition.
- Take omeprazole delayed-release capsules before a meal.
- Antacids may be taken with omeprazole delayed-release capsules.

Omeprazole Delayed-Release Capsules

- Swallow omeprazole delayed-release capsules whole. **Do not chew or crush omeprazole delayed-release capsules.**
- If you have trouble swallowing a whole capsule, you can open the capsule and take the contents in applesauce. See the "Instructions for Use" at the end of this Medication Guide for instructions on how to take omeprazole delayed-release capsules with applesauce.

If you miss 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 at your regular time. Do not take 2 doses at the same time to make up for the missed dose.

If you take too much omeprazole delayed-release capsules, call your doctor or your poison control center at 1-800-222-1222 right away or go to the nearest emergency room.

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

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

- **See "What is the most important information I should know about omeprazole delayed-release capsules?"**
- **Vitamin B-12deficiency**. Omeprazole delayed-release capsules reduce 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.** This problem can be serious. Low magnesium can happen in some people who take a PPI 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**	• **jitteriness**	• **spasms of the hands and feet**
• **dizziness**	• **jerking movements or shaking (tremors)**	• **cramps or muscle aches**
• **abnormal or fast heart beat**	• **muscle weakness**	• **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
- nausea
- vomiting
- stomach pain
- diarrhea
- 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 delayed-release capsules:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop omeprazole delayed-release capsules if these symptoms happen. Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects with omeprazole delayed-release capsules. For more information, ask your doctor or pharmacist. 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 20° to 25°C (68° to 77°F).
- Keep the container of omeprazole delayed-release capsules closed tightly.
- 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 the safe and effective use of 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.

What are the ingredients in omeprazole delayed-release capsules?

Active ingredient in omeprazole delayed-release capsules: omeprazole

Inactive ingredients in omeprazole delayed-release capsules: anhydrous lactose, cetyl alcohol, di-sodium hydrogen phosphate dihydrate, hypromellose, hypromellose phthalate, mannitol, simethicone emulsion 30%, sodium lauryl sulfate and sugar sphere.

The capsule shell for omeprazole delayed-release capsules USP, 20 mg contains FD&C Blue No.1, gelatin, sodium lauryl sulfate and titanium dioxide.

The imprinting ink has the following components: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide.

Manufactured by:

Glenmark Pharmaceuticals Limited

Colvale-Bardez, Goa 403 513, India

Manufactured for:

Glenmark Pharmaceuticals Inc., USA

Mahwah, NJ 07430

Questions? 1 (888)721-7115

www.glenmarkpharma.com/usa

December 2016

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

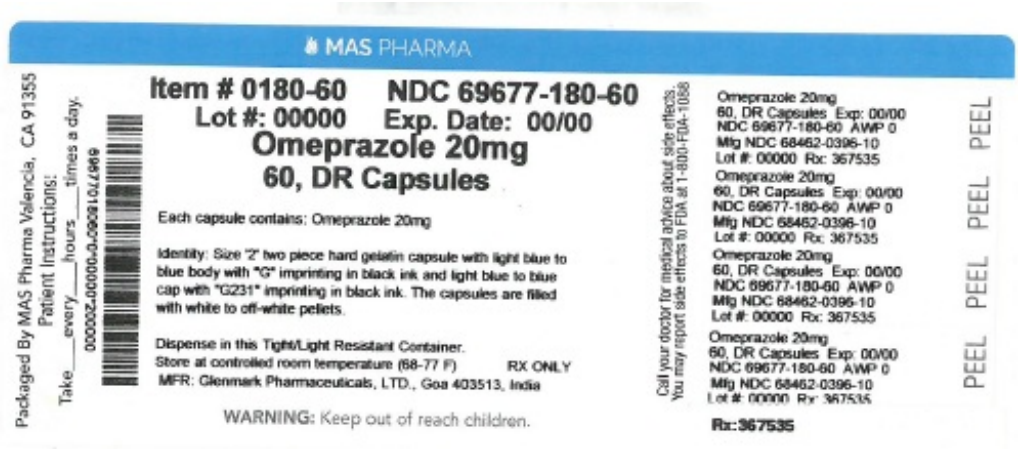
INSTRUCTIONS FOR USE

Omeprazole Delayed-Release Capsules USP
(oh mep' ra zole)

Omeprazole delayed-release capsules
Taking omeprazole delayed-release capsules with applesauce:

1. Place 1 tablespoon of applesauce into a clean container.
2. Carefully open the capsule and sprinkle the pellets onto the applesauce. Mix the pellets with the applesauce.
3. Swallow the applesauce and pellet mixture right away. Do not chew or crush the pellets. Do not store the applesauce and pellet mixture for later use.

OMEPRAZOLE DR 20MG CAPSULES



OMEPRAZOLE

omeprazole capsule, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69677-180(NDC:68462-396)
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**
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE (UNII: 94255I6E2T)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CETYL ALCOHOL (UNII: 936JST6JCN)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
HYPROMELLOSE PHTHALATE (31% PHTHALATE, 40 CST) (UNII: G4U024CQK6)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics			
Color	blue (light blue to blue body) , blue (light blue to blue cap)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	G;G231
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69677-180-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2014	
2	NDC:69677-180-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2014	
3	NDC:69677-180-01	120 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2014	
4	NDC:69677-180-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091672	10/31/2014	

Labeler - Mas Management Group, Inc. (079363782)

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Mas Management Group, Inc.