

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets safely and effectively. See full prescribing information for Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets

Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Warnings and Precautions, Hypomagnesemia (5.6) 05/2011
Warnings and Precautions, 11/2011
Diminished anti-platelet activity of clopidogrel (5.5)

INDICATIONS AND USAGE

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is a proton pump inhibitor indicated for:

- Treatment of duodenal ulcer (1.1)
- Treatment of gastric ulcer (1.2)
- Treatment of gastroesophageal reflux disease (GERD) (1.3)
- Maintenance of healing of erosive esophagitis (1.4)

DOSAGE AND ADMINISTRATION

- Short-Term Treatment of Active Duodenal Ulcer: 20 mg once daily for 4 weeks (some patients may require an additional 4 weeks of therapy (14.1))(22)
- Gastric Ulcer: 40 mg once daily for 4-8 weeks (2.3)
- Gastroesophageal Reflux Disease (GERD) (2.4)
 - Symptomatic GERD (with no esophageal erosions): 20 mg once daily for up to 4 weeks
 - Erosive Esophagitis: 20 mg once daily for 4-8 weeks
- Maintenance of Healing of Erosive Esophagitis: 20 mg once daily (2.5)

DOSAGE FORMS AND STRENGTHS

- Tablets 20 mg omeprazole, 750 mg sodium bicarbonate, and 343 mg magnesium hydroxide (3)
- Tablets 40 mg omeprazole, 750 mg sodium bicarbonate, and 343 mg magnesium hydroxide (3)

CONTRAINDICATIONS

- Known hypersensitivity to Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets or any components in the formulation (4)
- Patients who cannot take magnesium (4)

WARNINGS AND PRECAUTIONS

- Concomitant Gastric Malignancy: Symptomatic response to therapy with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets does not preclude the presence of gastric malignancy (5.1)
- Atrophic Gastritis: Has been observed in gastric corpus biopsies from patients treated long-term with omeprazole (5.2)
- Buffer Content: Contains sodium bicarbonate. (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)
- Diminished anti-platelet activity of clopidogrel due to impaired CYP2C19 function by 80 mg omeprazole (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 2%) are: Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence (6)
To report SUSPECTED ADVERSE REACTIONS, contact Santarus Inc. at 1-888-778-0887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs metabolized by cytochrome P450 (e.g., diazepam, warfarin, phenytoin, cyclosporine, disulfiram, benzodiazepines): Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets can prolong their elimination. Monitor to determine the need for possible dose adjustments when taken with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets (7)
- Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time (7)
- Drugs for which gastric pH can affect bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, and digoxin): Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may interfere with absorption due to inhibition of gastric acid secretion (7)
- Voriconazole: May increase plasma levels of omeprazole (7)
- Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may reduce plasma levels of atazanavir and nelfinavir (7)
- Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may increase serum levels of tacrolimus, voriconazole, saquinavir, and clarithromycin (7)
- Co-administration of clopidogrel with 80 mg omeprazole may reduce the pharmacological activity of clopidogrel if given concomitantly or if given 12 hours apart (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based upon animal data, may cause fetal harm (8.1)
- The safety and effectiveness of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets in pediatric patients less than 18 years of age have not been established. (8.4)
- Hepatic Impairment: Consider dose reduction, particularly for maintenance of healing of erosive esophagitis (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA Approved Patient Labeling.

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Duodenal Ulcer
- 1.2 Gastric Ulcer
- 1.3 Treatment of Gastroesophageal Reflux Disease (GERD)
- 1.4 Maintenance of Healing of Erosive Esophagitis

2 DOSAGE AND ADMINISTRATION

- 2.1 Instructions for Use
- 2.2 Short-Term Treatment of Active Duodenal Ulcer
- 2.3 Gastric Ulcer
- 2.4 Gastroesophageal Reflux Disease (GERD)
- 2.5 Maintenance of Healing of Erosive Esophagitis
- 2.6 Use with clopidogrel

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Concomitant Gastric Malignancy
- 5.2 Atrophic Gastritis
- 5.3 Buffer Content
- 5.4 Bone Fracture
- 5.5 Diminished anti-platelet activity of clopidogrel due to impaired CYP2C19 function by omeprazole
- 5.6 Hypomagnesemia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

7 DRUG INTERACTIONS

- 7.1 Drugs metabolized by cytochrome P450 (CYP)
- 7.2 Drugs for which gastric pH can affect bioavailability
- 7.3 Antiretroviral Agents

7.4 Antimicrobials

7.5 Clopidogrel

7.6 Tacrolimus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

8.8 Asian Population

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Duodenal Ulcer Disease

14.2 Gastric Ulcer

14.3 Gastroesophageal Reflux Disease (GERD)

14.4 Long Term Maintenance Treatment of Erosive Esophagitis

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Duodenal Ulcer

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. [See *Clinical Studies (14.1)*]

1.2 Gastric Ulcer

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. [See *Clinical Studies (14.2)*]

1.3 Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is indicated for the treatment of heartburn and other symptoms associated with GERD. [See *Clinical Studies (14.3)*]

Erosive Esophagitis

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis that has been diagnosed by endoscopy.

The efficacy of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets used for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g., heartburn), additional 4-8 week courses of omeprazole may be considered. [See *Clinical Studies (14.3)*]

1.4 Maintenance of Healing of Erosive Esophagitis

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months. [See *Clinical Studies (14.4)*]

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Use

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide is available as tablets in 20 mg and 40 mg strengths of omeprazole for oral administration in adult patients 18 years and older.

All recommended doses throughout the labeling are based upon omeprazole. Since both the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg), two 20 mg tablets are not equivalent to one 40 mg tablet; therefore, two 20 mg tablets should not be substituted for one 40 mg tablet.

Because Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets contain magnesium hydroxide, the tablets should not be substituted for ZEGERID products (e.g., ZEGERID Powder for Oral Suspension or ZEGERID Capsules).

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets should be taken on an empty stomach with water at least one hour before a meal. Do not use other liquids.

2.2 Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is 20 mg once daily. Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.

2.3 Benign Gastric Ulcer

The recommended adult oral dose of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is 40 mg once daily for 4-8 weeks.

2.4 Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal erosions is 20 mg once daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis is 20 mg once daily for 4-8 weeks.

2.5 Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is 20 mg once daily.

2.6 Use with clopidogrel

Avoid concomitant use of clopidogrel and omeprazole. Coadministration of clopidogrel with 80 mg omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel if given concomitantly or if given 12 hours apart [see *Warnings and Precautions (5.6) and Drug Interactions (7)*]

3 DOSAGE FORMS AND STRENGTHS

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, 20 mg, are white oval-shaped tablets. One side of each tablet is embossed with "ZM 20." Each tablet contains 20 mg omeprazole and 750 mg sodium bicarbonate plus 343 mg magnesium hydroxide.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, 40 mg, are white oval-shaped tablets. One side of each tablet is embossed with "ZM 40." Each tablet contains 40 mg omeprazole and 750 mg sodium bicarbonate plus 343 mg magnesium hydroxide.

4 CONTRAINDICATIONS

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is contraindicated in patients with known hypersensitivity to any components of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, interstitial nephritis, and urticaria.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is contraindicated in patients who cannot take magnesium. [See *Warnings and Precautions (5.3)*]

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 Buffer Content

Each 20 mg and 40 mg Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablet contains 750 mg (9 mEq) of sodium bicarbonate (equivalent to 209 mg of Na⁺) and 343 mg (12 mEq) of magnesium hydroxide (equivalent to 143 mg of Mg²⁺).

Sodium Bicarbonate

Because Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets contains sodium bicarbonate, it should be used with caution in patients with Bartter's syndrome, hypokalemia, hypocalcemia, respiratory and metabolic alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

The sodium content of this product should be taken into consideration when administering to patients on a sodium-restricted diet or at risk of developing congestive heart failure (CHF).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase.

Magnesium Hydroxide

Because Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets contains magnesium hydroxide, it should be used with caution in elderly and in patients with renal impairment or renal disease due to increased risk of developing hypermagnesemia and magnesium toxicity. Magnesium hydroxide should not be used in patients with renal failure unless serum magnesium levels are being closely monitored.

Hypermagnesemia has been reported in infants whose mothers were using magnesium-containing antacid products chronically in high doses.

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 the established treatment guidelines. [See *Dosage and Administration (2) and Adverse Reactions (6.2)*]

5.5 Diminished Anti-platelet Activity of clopidogrel due to Impaired CYP2C19 Function by Omeprazole

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 interfere with CYP2C19 activity. Avoid concomitant use of clopidogrel and omeprazole. Co-administration of clopidogrel with 80 mg omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel if given concomitantly or if given 12 hours apart [see *Drug Interactions* (7)].

5.6 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* (6.2)]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 clinical practice.

In the U.S clinical trial population, of 465 patients, the adverse reactions summarized in Table 1 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse reactions considered by investigators as possibly, probably, or definitely related to the drug.

Table 1: Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy from U.S. Studies

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The international clinical trials were double-blind and open-label in design.

Table 2: Incidence of Adverse Reactions ≥ 1% Causal Relationship Not Assessed from International Studies

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a whole, site unspecified		
Abdominal Pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid Regurgitation	1.9	3.3
Nervous System / Psychiatric		
Headache	2.9	2.5

The most common adverse reactions reported (i.e., with an incidence rate ≥ 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 of ≥ 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.

6.2 Post-marketing 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.

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

Endocrine: Gynecomastia.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, stomatitis, abdominal swelling, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastrointestinal carcinoids have been reported in patients with Zollinger-Ellison 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).

Metabolism and Nutritional Disorders: Hypoglycemia, hyponatremia, hypomagnesemia, weight gain.

Musculoskeletal: Muscle weakness, myalgia, muscle cramps, joint pain, bone fracture, and leg pain.

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

Respiratory: Epistaxis, pharyngeal pain.

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

Special Senses: Tinnitus, taste perversion.

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

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

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

7 DRUG INTERACTIONS

7.1 Drugs metabolized by cytochrome P450 (CYP)

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 / Sodium Bicarbonate / Magnesium Hydroxide Tablets.

7.2 Drugs for which gastric pH can affect bioavailability

Because of its inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, and digoxin). In the clinical efficacy trials acidants were used concomitantly with the administration of 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. When voriconazole (400 mg every 12 hours for one day, then 200 mg for 6 days) was given with omeprazole (40 mg once daily for 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.

7.3 Antiretroviral Agents

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect. 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. 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 hours 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. 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. 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.

7.4 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-hydroxylclarithromycin 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-hydroxylclarithromycin, 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 3: Clarithromycin Tissue Concentrations
2 hours after Dose¹

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

¹Mean ± (μg/g)

7.5 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 [*see Warnings and Precautions (5.6)*].

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. The active metabolite of clopidogrel selectively and irreversibly inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor, thereby inhibiting platelet aggregation. The mean inhibition of platelet aggregation at 5 mM ADP was diminished by 39% (Day 1) and 21% (Day 5) when clopidogrel and omeprazole were administered together.

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 [*see Warnings and Precautions (5.6)*].

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.

7.6 Tacrolimus

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent versus chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).¹

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H₂-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, 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.² In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. 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 the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H₂-blockers or omeprazole in the first trimester (134 exposed to omeprazole).³ The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).⁴ The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

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.

Hypermagnesemia has been reported in infants whose mothers were using magnesium-containing antacid products chronically in high doses.

Reproduction studies conducted with omeprazole in rats at oral doses up to 28 times the human dose of 40 mg/day (based on body surface area) and in rabbits at doses up to 28 times the human dose (based on body surface area) did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 2.8 to 28 times the human dose of 40 mg /day (based on body surface area) produced dose-related increases in embryo-letality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 2.8 to 28 times the human dose (based on body surface area), dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring. [See *Nonclinical Toxicology (13.2)*]

There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

8.3 Nursing Mothers

Omeprazole concentrations have been 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. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate and magnesium hydroxide should be used with caution in nursing mothers.

8.4 Pediatric Use

The safety and effectiveness of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets in pediatric patients less than 18 years of age have not been established.

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 with buffered omeprazole 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 subjects). The plasma half-life averaged one hour, about twice that in nonelderly, healthy subjects taking Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets. 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 dose reduction is necessary. However, Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets contains magnesium hydroxide (143 mg of Mg²⁺); therefore, magnesium levels should be closely monitored when using this product in patients with renal impairment. [See *Clinical Pharmacology (12.3)*]

8.8 Asian Population

Recommend 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, a certified regional poison control center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

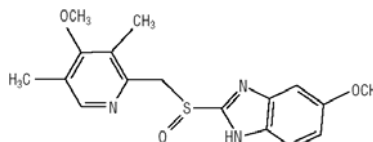
Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures.

Similarly, a magnesium overdose may lead to hypermagnesemia. Hypermagnesemia results in a depressant effect on the central nervous system, causing anorexia and nausea, and neuromuscular system. Magnesium toxicity causes hypotension, muscle weakness, and electrographic changes.

11 DESCRIPTION

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate plus magnesium hydroxide, both of which are antacids. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is C₁₇H₁₉N₃O₃S, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is available in two strengths, 20 mg and 40 mg of omeprazole, and is formulated as an immediate-release tablet for oral administration. Each tablet contains either 20 mg or 40 mg of omeprazole (not enteric coated), 750 mg of sodium bicarbonate and 343 mg of magnesium hydroxide with the following inactive ingredients: hydroxypropyl cellulose, croscarmellose sodium, sodium stearyl fumarate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is an immediate-release tablet formulation that contains antacid components (sodium bicarbonate plus magnesium hydroxide), which raise the gastric pH and thus protects omeprazole from acid degradation.

12.2 Pharmacodynamics

Antisecretory Activity: Results from PK/PD studies of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of a previous

FDA-approved formulation of ZEGERID with Magnesium Hydroxide in healthy subjects were as follows.

Table 4: Effect of ZEGERID® with Magnesium Hydroxide Chewable Tablets on Intra-gastric pH on Day 7

Parameter	Omeprazole/Sodium Bicarbonate/ Magnesium Hydroxide	
	40 mg/600 mg/ 700 mg (n = 35)	20 mg/600 mg/ 700 mg (n = 29)
% Decrease from Baseline for Integrated Gastric Acidity (mmol*hr/L)	73%	72%
Coefficient of variation	19%	28%
% Time Gastric pH > 4 (Hours)	62% (14.9 h)	57% (13.8 h)
Coefficient of variation	30%	32%
Median pH	5.1	4.8
Coefficient of variation	24%	29%

Note: Values are medians. All parameters were measured over a 24-hour period.

The antisecretory effect of omeprazole lasts longer than would be expected from the short (1 hour) plasma half-life, apparently due to irreversible binding to the parietal H⁺/K⁺ ATPase enzyme.

Enterochromaffin-like (ECL) Cell Effects: In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [See *Nonclinical Toxicology (13.1)*]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H₂-receptor antagonists. Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. These studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects: In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H₂-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold versus 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects: Systemic effects of omeprazole in the CNS, cardiovascular, and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin, or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single intravenous 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 (12.2)*]

12.3 Pharmacokinetics

Absorption: When Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is administered on an empty stomach at least 1 hour prior to a meal, the absorption of omeprazole is rapid, with a mean peak plasma level of omeprazole being 1528 ng/mL and time to peak of approximately 41 minutes (range 10-120 min) after a single-dose administration.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from ZEGERID are approximately proportional from 20 to 40 mg doses of omeprazole, but a greater than linear mean AUC (three-fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole from ZEGERID increases upon repeated administration.

When a previous FDA-approved formulation of ZEGERID with Magnesium Hydroxide is administered 1 hour after a meal, the AUC is reduced by approximately 22% relative to administration 1 hour prior to a meal.

Distribution: Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism: Following single dose oral administration of omeprazole, the majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been 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.

Excretion: Following single dose oral administration of omeprazole, little if any, unchanged drug is excreted in urine. The mean plasma omeprazole half-life in healthy subjects is approximately 1 hour (range 0.4 to 3.1 hours) and the total body clearance is 500-600 mL/min.

Special Populations

Geriatric

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 subjects, versus 58% in young subjects 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 subjects) and its plasma half-life averaged one hour, about twice that of young healthy subjects.

Pediatric

The pharmacokinetics of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets has not been studied in patients < 18 years of age.

Gender

There are no known differences in the absorption or excretion of omeprazole between males and females.

Hepatic Insufficiency

In patients with chronic hepatic disease, the bioavailability of omeprazole from a buffered solution increased to approximately 100% compared to an intravenous dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 0.5-1 hour in normal subjects. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects. Dose reduction, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired should be considered.

Renal Insufficiency

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m², the disposition of omeprazole from a buffered solution was very similar to that in healthy subjects, 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.

However, Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets contains magnesium hydroxide (143 mg of Mg²⁺); therefore, magnesium levels should be closely monitored when using this product 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 to Caucasians. Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for Asian subjects should be considered.

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 (approximately 0.35 to 28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated versus 10% controls). By the second year the difference between treated and control rats was much smaller (46% versus 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 3.3 times the human dose of 40 mg/day, based on body surface area). 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 and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). 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.

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.

Omeprazole at oral doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on the fertility and general reproductive performance in rats.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproduction studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) 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 2.8 to 28 times the human dose of 40 mg/day, based on body surface area).

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 a day than with placebo ($p \leq 0.01$).

Table 5: 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

* ($p \leq 0.01$)

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 a day than with ranitidine 150 mg twice daily ($p < 0.01$).

Table 6: Treatment of Active Duodenal Ulcer % of Patients Healed

	Omeprazole 20 mg a.m. (n = 145)	Ranitidine 150 mg twice daily (n = 148)
Week 2	42	34
Week 4	82*	63

* ($p < 0.01$)

Healing occurred significantly faster in patients treated with omeprazole than in those treated with ranitidine 150 mg twice daily ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 40 mg and 20 mg of omeprazole were compared to 150 mg twice daily 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.

Table 7: Treatment of Active Duodenal Ulcer % of Patients Healed

	Omeprazole 40 mg (n = 36)	Omeprazole 20 mg (n = 34)	Ranitidine 150 mg twice daily (n = 35)
Week 2	83*	83*	53
Week 4	100*	97*	82
Week 8	100	100	94

* ($p \leq 0.01$)

14.2 Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Table 8: Treatment of Gastric Ulcer % of Patients Healed (All Patients Treated)

	Omeprazole 40 mg once daily (n = 214)	Omeprazole 20 mg once daily (n = 202)	Placebo (n = 104)
Week 4	55.6**	47.5**	30.8
Week 8	82.7**,+	74.8**	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 a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

**Table 9: Treatment of Gastric Ulcer
% of Patients Healed (All Patients Treated)**

	Omeprazole 40 mg once daily (n = 187)	Omeprazole 20 mg once daily (n = 200)	Ranitidine 150 mg twice daily (n = 199)
Week 4	78.1***++	63.5	56.3
Week 8	91.4***++	81.5	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.

Table 10: % 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

Erosive Esophagitis

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

Table 11: % Patients Healed

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

14.4 Long Term Maintenance Treatment 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 in Table 12.

Table 12: 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 to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table

below provides the results of this study for maintenance of healing of erosive esophagitis.

Table 13 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

Percent in endoscopic remission at 12 months

* (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.

15 REFERENCES

- Friedman JM and Polifka JE. Omeprazole. In: Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS). 2nd ed. Baltimore, MD: The Johns Hopkins University Press 2000; p. 516.
- Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. *Eur Obstet Gynecol Reprod Biol* 2001; 96(1):63-8.
- Ruigómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; 150:476-81.
- Lalkin A, Loebstein, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998; 179:727-30.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, 20 mg, are white oval-shaped tablets, 19 mm long, 9 mm wide, and 7 mm thick, embossed with “ZM20” on one side. They are supplied as follows:

NDC 68012-202-30: Bottles of 30 tablets

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, 40 mg, are white oval-shaped tablets, 19 mm long, 9 mm wide, and 7 mm thick, embossed with “ZM40” on one side. They are supplied as follows:

NDC 68012-204-30: Bottles of 30 tablets

Storage

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

Keep this medication out of the hands of children. Keep container tightly closed. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

Instruct patients to take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets on an empty stomach at least one hour prior to a meal. [See *Dosage and Administration* (2.1)]

Instruct patients to swallow Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets with water. Patients should not use other liquids. [See *Dosage and Administration* (2.1)]

Patients should be instructed to not substitute two 20 mg tablets for one 40 mg tablet because the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg). Substituting two 20 mg tablets for one 40 mg tablet would result in the patient receiving twice as much sodium bicarbonate and magnesium hydroxide. [See *Dosage and Administration* (2.1)]

Patients should be instructed not to substitute Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for any ZEGERID dosage forms because different dosage forms contain different amounts of sodium bicarbonate and magnesium hydroxide. [See *Dosage and Administration* (2.1)]

Patients should be advised that this drug is not approved for use in patients less than 18 years of age. [See *Pediatric Use* (8.4)]

**This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>**

Patients on a sodium-restricted diet or patients at risk of developing congestive heart failure (CHF) should be informed of the sodium content of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets (209 mg per tablet). Patients should be informed that chronic use of sodium bicarbonate may cause problems and increased sodium intake can cause swelling and weight gain. If this occurs, they should contact their healthcare provider. *[See Warnings and Precautions (5.3)]*

Patients should be informed that the most frequent adverse reactions associated with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets include headache, abdominal pain, nausea, diarrhea, vomiting and flatulence. *[See Adverse Reactions (6)]*

Pregnant women should be advised that a harmful effect of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets on the fetus can not be ruled out and that the drug should be used with caution during pregnancy. *[See Pregnancy (8.1)]*

Patients should be advised to use this drug with caution if they are regularly taking calcium supplements. *[See Warnings and Precautions (5.3)]*

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 (5.5)]*

Manufactured for Santarus, Inc., San Diego, CA 92130 • 1-888-778-0887
by: Norwich Pharmaceuticals, Inc., Norwich, NY 13814



ZEGERID® is a trademark of Santarus, Inc.

© 2011 Santarus, Inc.

FDA-APPROVED PATIENT LABELING

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets

Read the Patient Information that comes with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets is a medicine called a proton pump inhibitor (PPI). Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets reduce the amount of acid in your stomach.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets are used in adults for:

- for 4 weeks to heal ulcers in the first part of the small bowel (duodenal ulcers). Your doctor may prescribe an additional 4 weeks of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.
- 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 is a chronic condition (lasts a long time) that occurs when acid from the stomach backs up into the esophagus (food pipe) causing symptoms, such as heartburn, or damage to the lining of the esophagus. Common symptoms include frequent heartburn that will not go away, a sour or bitter taste in the mouth, and difficulty swallowing.

- 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. Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets has not been studied for treatment lasting longer than 12 months (1 year)

It is not known if Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets are safe and effective in children and adolescents less than 18 years of age.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

Who should not take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

Do not take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets if you:

- are allergic to any of the ingredients in Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets. See the end of this leaflet for a complete list of ingredients in Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.
- are allergic to any other PPI medicine.

What should I tell my doctor before I take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

Before you take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, tell your doctor if you:

- have been told that you have low magnesium levels in your blood.
- have any liver problems.
- have heart failure.
- have Bartter's syndrome (a rare kidney disorder).
- have any allergies.
- are pregnant or planning to become pregnant. It is not known if Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets can harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or planning to breastfeed. You and your doctor should decide if you will take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets or breastfeed. You should not do both. Sodium bicarbonate (a part of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets) should be used with caution in nursing mothers.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may affect how other medicines work, and other medicines may affect how Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets work. This can cause serious side effects. Know the medicines that you take. Keep a list of them with you and show it to your doctor when you get a new medicine. Be sure to tell your doctor if you are taking:

- diazepam (Valium)®
- warfarin (Coumadin, Jantoven)®
- phenytoin (Dilantin)®
- cyclosporine
- disulfiram (Antabuse)®
- benzodiazepines
- ketoconazole (Nizoral)®
- ampicillin sodium (Unazyn)® or ampicillin trihydrate (Principen)®
- iron salts
- digoxin
- voriconazole (Nizoral)®
- atazanavir (Reyataz)®
- nelfinavir (Viracept)®
- tacrolimus (Prograf)®
- saquinavir (Fortovase)®
- clarithromycin
- clopidogrel (Plavix)

How should I take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

- Take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets exactly as prescribed by your doctor. Do not change your dose or stop taking Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets without talking to your doctor. Take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for as long as it is prescribed even if you feel better.
- Take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets on an empty stomach at least one hour before a meal.
- Swallow Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets whole with water. **DO NOT USE OTHER LIQUIDS.** Do not crush or chew.
- Do not substitute Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for other ZEGERID dosage forms because different dosage forms contain different amounts of sodium bicarbonate and magnesium hydroxide.
- If you forget to take a dose of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, 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 two doses to make up for a missed dose.
- If you take too much Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets, call your doctor or Poison Control Center right away, or go to the emergency room.
- Your doctor may prescribe antibiotic medicines with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets to help treat a stomach infection and heal stomach-area (duodenal) ulcers that are caused by bacteria called *H. pylori*. Make sure you read the patient information that comes with an antibiotic before you start taking it.

What are the possible side effects of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may cause serious allergic reactions. See the end of this leaflet for a complete list of ingredients in Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.

- **Serious allergic reactions.** Tell your doctor if you get any of the following symptoms with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.
 - rash
 - face swelling
 - throat tightness
 - difficulty breathing

Your doctor may stop Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets if these symptoms happen.

- **Low magnesium levels in your body.** This problem can be serious. 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 have 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 / Sodium Bicarbonate / Magnesium Hydroxide Tablets or, during treatment if you will be taking Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for a long period of time.

The most common side effects with Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets include:

- headache
- abdominal pain
- nausea
- diarrhea,
- vomiting
- gas

Using Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for a long time may cause problems like swelling and weight gain. Tell your doctor if this happens.

If you are on a low sodium diet or at risk of developing congestive heart failure (CHF), you and your doctor should decide if you will take Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets.

If you are elderly or have kidney problems, the magnesium content of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets may raise the amount of magnesium in your body higher than normal amounts.

People who are taking multiple daily doses of proton pump inhibitor medicines for a long period of time may have an increased risk of fractures of the hip, wrist or spine.

Tell your doctor about any side effects that bother you or that do not go away. These are not all the possible side effects of Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

- Store Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets in a dry place at room temperature, 59 °F to 86 °F (15 °C to 30 °C).

Keep Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets and all medicines out of the reach of children.

General Information about Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets

**This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>**

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets for any condition for which it was not prescribed by your doctor. Do not give Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets to other people, even if they have the same symptoms as you. It may harm them.

This leaflet summarizes the most important information about Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information about Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets that is written for healthcare professionals. For full product information, visit the website at <http://www.santarus.com> or call the toll-free number 1-888-778-0887.

What are the ingredients in Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets?

Active Ingredients: omeprazole / sodium bicarbonate / magnesium hydroxide

Inactive ingredients: hydroxypropyl cellulose, croscarmellose sodium, sodium stearyl fumarate.

For prescription only

Revised November 2011

ZEGERID® is a registered trademark of Santarus, Inc.

Omeprazole / Sodium Bicarbonate / Magnesium Hydroxide Tablets are manufactured for Santarus, Inc., San Diego, CA 92130 by: Norwich Pharmaceuticals, Inc., Norwich, NY 13814

For more information call 1-888-778-0887

©2011 Santarus, Inc.