HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEGERID® with Magnesium Hydroxide Chewable Tablets safely and effectively. See full prescribing information for ZEGERID with Magnesium Hydroxide Chewable Tablets.

ZEGERID with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Chewable Tablets
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
ZEGERID with Magnesium Hydroxide Chewable 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)

The safety and effectiveness of ZEGERID with Magnesium Hydroxide Chewable Tablets in pediatric patients (<18 years of age) have not been established. (8.3)

----------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)) (2)
- Gastric Ulcer: 40 mg once daily for 4-8 weeks (2)
- Gastroesophageal Reflux Disease (GERD) (2)
  - 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)

----------DOSAGE FORMS AND STRENGTHS----------
- ZEGERID with Magnesium Hydroxide Chewable Tablets (omeprazole/sodium bicarbonate/magnesium hydroxide) is available in 20 and 40 mg strengths (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to ZEGERID or any of the components in the formulation
- Patients who can not take Magnesium

----------WARNINGS AND PRECAUTIONS----------
- Concomitant Gastric Malignancy: Symptomatic response to therapy with ZEGERID with Magnesium Hydroxide Chewable 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 (5.3):
  Sodium content to be taken into consideration when administering to patients on a sodium-restricted diet
  Magnesium content increases risk of hypermagnesemia and magnesium toxicity in neonates, elderly, and in patients with renal impairment or renal disease
  To be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance because of its sodium bicarbonate content; long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 2%) are:
Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence (6)

To report SUSPECTED ADVERSE REACTIONS, contact Santarus Inc. at 1-888-778-0887, option 2 or http://www.santarus.com/contact/, 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): ZEGERID with Magnesium Hydroxide Chewable Tablets can prolong their elimination. Monitor to determine the need for possible dose adjustments when taken with ZEGERID with Magnesium Hydroxide Chewable 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): ZEGERID with Magnesium Hydroxide Chewable Tablets may interfere with absorption due to inhibition of gastric acid secretion (7)
- Voriconazole: May increase plasma levels of omeprazole (7)
- ZEGERIDwith Magnesium Hydroxide may reduce plasma levels of atazanavir and nelfinavir (7)
- ZEGERIDwith Magnesium Hydroxide may increase serum levels of tacrolimus, voriconazole, saquinavir, and clarithromycin (7)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based upon animal data, may cause fetal harm (8.1)
- The safety and effectiveness of ZEGERID with Magnesium Hydroxide in pediatric patients less than18 years of age have not been established. (8.4)
- Hepatic Impairment: Consider dose reduction, particularly for maintenance of healing of erosive esophagitis (12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: January 2010

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Duodenal Ulcer

ZEGERID® with Magnesium Hydroxide 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

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

Erosive Esophagitis
ZEGERID with Magnesium Hydroxide is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

The efficacy of ZEGERID with Magnesium Hydroxide 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

ZEGERID with Magnesium Hydroxide 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

ZEGERID with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) is available as chewable tablets in 20 mg and 40 mg strengths for adult use. Directions for use for each indication are summarized in Table 1.

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 (600 mg) and magnesium hydroxide (700 mg), two 20 mg chewable tablets are not equivalent to one 40 mg tablet; therefore, two 20 mg tablets should not be substituted for one 40 mg tablet. Conversely a half of one 40mg tablet should not be substituted for one 20 mg tablet.

Because ZEGERID with Magnesium Hydroxide chewable tablets contain Magnesium Hydroxide, the chewable tablets should not be substituted for other ZEGERID dosage forms (e.g., ZEGERID Powder for Oral Suspendion or ZEGERID Capsules).

ZEGERID with Magnesium Hydroxide should be taken on an empty stomach at least one hour before a meal.

Table 1: Recommended Doses of Zegerid with Magnesium Hydroxide by Indication for Adults 18 Years and Older

Indication	Recommended Dose	Frequency
Short-Term Treatment of Active Duodenal Ulcer	20 mg	Once daily for 4 weeks*,+
Benign Gastric Ulcer	40 mg	Once daily for 4-8 weeks **,+
Gastroesophageal Reflux Disease (GERD)		
Symptomatic GERD	20 mg	Once daily for up to 4 weeks+
(with no esophageal erosions)	20 mg	Once daily for 4-8 weeks+
Erosive Esophagitis		
Maintenance of Healing of Erosive Esophagitis	20 mg	Once daily**

* Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy. *[See Clinical Studies (14.1)]*
** For additional information, *[See Clinical Studies (14)]*.
\+ For additional information, *[See Indications and Usage (1)]*.

Special Populations

Hepatic Insufficiency
Consider dose reduction, particularly for maintenance of healing of erosive esophagitis. *[See Clinical Pharmacology (12.3)]*

Administration of Chewable Tablets

ZEGERID with Magnesium Hydroxide chewable tablets should be chewed and swallowed with water. **DO NOT SWALLOW WHOLE.** DO NOT USE OTHER LIQUIDS. **DO NOT SUBSTITUTE FOR OTHER ZEGERID DOSAGE FORMS.**

3 DOSAGE FORMS AND STRENGTHS

ZEGERID with Magnesium Hydroxide 20-mg Chewable Tablets: Each pink, 18 mm in diameter, round tablet, inscribed with the number “2031” on one side and the Santarus logo on the other side, contains 20 mg omeprazole and 600 mg sodium bicarbonate plus 700 mg magnesium hydroxide.

ZEGERID with Magnesium Hydroxide 40-mg Chewable Tablets: Each pink, 18 mm in diameter, round tablet, inscribed with the number “4031” on one side and the Santarus logo on the other side, contains 40 mg omeprazole and 600 mg sodium bicarbonate plus 700 mg magnesium hydroxide.

4 CONTRAINDICATIONS

ZEGERIDwith Magnesium Hydroxide 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.

ZEGERID with Magnesium Hydroxide 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 ZEGERIDwith Magnesium Hydroxide chewable tablet contains 600 mg (7 mEq) of sodium bicarbonate (equivalent to 164 mg of Na+) and 700 mg (24 mEq) of magnesium hydroxide (equivalent to 292 mg of Mg++).

Sodium Bicarbonate

The sodium content of this product should be taken into consideration when administering to patients on a sodium-restricted diet.

Because ZEGERID products contain sodium bicarbonate, they should be used with caution in patients with Bartter's syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome

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

Magnesium Hydroxide

Because ZEGERID with Magnesium Hydroxide contains magnesium hydroxide, it should be used with caution in,the elderly and 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.

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 2 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 2: Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy

	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 (1.6)	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

Table 3 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2,631 patients and subjects received omeprazole.

Table 3: Incidence of Adverse Reactions ≥ 1% Causal Relationship not Assessed

	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

6.2 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

Cardiovascular
Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal
Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. 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 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)

Metabolic/Nutritional
Hyponatremia, hypoglycemia, and weight gain.

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

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

Respiratory
Epistaxis, pharyngeal pain.

Skin
Severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.

Special Senses
Tinnitus, taste perversion.

Ocular
Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

Urogenital
Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

Hematologic
Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate include metabolic alkalosis, seizures, and tetany.

The use of magnesium hydroxide is associated with diarrhea, abdominal cramping, chalky taste, diuresis, dehydration, nausea, and vomiting.

7 DRUG INTERACTIONS

Drugs for which gastric pH can affect bioavailability

Because of itsinhibition 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, and iron salts). In the clinical efficacy trials antacids were used concomitantly with the administration of omeprazole.

Drugs metabolized by cytrochrom 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 P-450 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 ZEGERIDwith Magnesium Hydroxide.

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 Cmax 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.

Antiretroviral Agents
Concomitant administration 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 reduct 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%, Cmax by 37% and 89% and Cmin 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%, Cmax by 96%, and Cmin 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 Cmax by 75% and in Cmin 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.

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 (Cmax, AUC0-24, and T1/2 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-hydroxyclarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean Cmax was 10% greater, the mean Cmin 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-hydroxyclarithromycin, the mean Cmax was 45% greater, the mean Cmin 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

Tissue	2 hours after Dose[1] 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)

[1]Mean ± (μg/g)

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-lethality, 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 Animal Toxicology and/or Pharmacology (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, ZEGERID with Magnesium Hydroxide Chewable 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 should be used with caution in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of ZEGERID with Magnesium Hydroxide Chewable Tablets have not been established in pediatric patients.less than 18 years of age.

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 ZEGERID with Magnesium Hydroxide. 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, ZEGERID with Magnesium Hydroxide chewable tablets contains 700mg (24mEq) magnesium hydroxide (equivalent to 292 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.

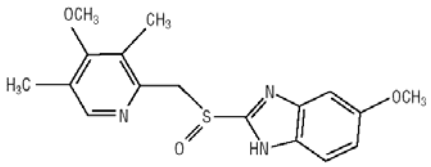
Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

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

ZEGERID® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) 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]-1*H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



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.

ZEGERID with Magnesium Hydroxide chewable tablets are available in two strengths containing 40 mg and 20 mg of omeprazole, and is formulated as an immediate-release chewable tablet. Each chewable tablet contains either 40 mg or 20 mg of omeprazole and 600 mg of sodium bicarbonate plus 700 mg of magnesium hydroxide with the following inactive ingredients: hydroxypropyl cellulose, croscarmellose sodium, xylitol, sucralose, flavoring, magnesium stearate, and FD&C Red #40 Aluminum Lake.

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. ZEGERID with Magnesium Hydroxide is an immediate-release chewable tablet formulation that contains an antacid component (sodium bicarbonate plus magnesium hydroxide) which raises 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 ZEGERID with Magnesium Hydroxide chewable tablets in healthy subjects are shown in Table 4 below.

Table 4: Effect of ZEGERID® with Magnesium Hydroxide on Intragastric Ph, Day 7

	Omeprazole/Sodium Bicarbonate/ Magnesium Hydroxide	
Parameter	**40 mg/600 mg/ 700 mg (n = 35)**	**20 mg/600 mg/ 700 mg (n = 29)**
% Decrease from Baseline for Integrated Gastric	73%	72%

Acidity (mmol*hr/L)		
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 very 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 vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

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

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

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

12.3 Pharmacokinetics

Absorption
When ZEGERID with Magnesium Hydroxide chewable tablets are 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 (%CV) of omeprazole being 1763 ng/mL (25%) and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from ZEGERID with Magnesium Hydroxide are approximately proportional to those 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 with Magnesium Hydroxide increases upon repeated administration.

When ZEGERID with Magnesium Hydroxide chewable tablets are 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, similar to that of young healthy subjects.

Pediatric
The pharmacokinetics of ZEGERID with Magnesium Hydroxide have 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 I.V. 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 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 m^2, 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.

ZEGERID with Magnesium Hydroxide chewable tablets contain magnesium hydroxide (292 mg of Mg++); therefore, magnesium levels should be closely monitored when using this product in patients with renal failure.

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 H_2-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 ($p \leq 0.01$). (See Table 5)

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 b.i.d. ($p < 0.01$). (See Table 6)

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

	Omeprazole 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d. (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 b.i.d. ($p < 0.01$).

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 a day 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. (See Table 7)

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

	Omeprazole 40 mg (n = 36)	Omeprazole 20 mg (n = 34)	Ranitidine 150 mg b.i.d. (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. (See Table 8)

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

	Omeprazole 40 mg q.d. (n = 214)	Omeprazole 20 mg q.d. (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. (See Table 9)

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

	Omeprazole 40 mg q.d. (n = 187)	Omeprazole 20 mg q.d (n = 200)	Ranitidine 150 mg b.i.d. (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. Results are shown in Table 10.

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 shown in Table 11.

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 q.d. (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 q.d. 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. Table 13 provides the results of this study for maintenance of healing of erosive esophagitis.

Table 13: Life Table Analysis

	Omeprazole 20 mg q.d. (n = 131)	Omeprazole 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	77*	58‡	46

* (p = 0.01) Omeprazole 20 mg q.d. versus Omeprazole 10 mg q.d. or Ranitidine.
‡ (p = 0.03) Omeprazole 10 mg q.d. 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

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3. Ruigómez A, Rodriquez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; 150: 476-81.
4. 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

ZEGERID with Magnesium Hydroxide 20-mg Chewable Tablets: Each pink, 18 mm in diameter, round tablet, inscribed with the number:"2031" on one side and the Santarus logo on the other side, contains 20 mg omeprazole and 600 mg sodium bicarbonate plus 700 mg magnesium hydroxide.

NDC 68012-152-30 Bottles of 30 chewable tablets

ZEGERID with Magnesium Hydroxide 40-mg Chewable Tablets: Each pink, 18 mm in diameter, round tablet, inscribed with the number "4031" on one side and the Santarus logo on the other side, contains 40 mg omeprazole and 600 mg sodium bicarbonate plus 700 mg magnesium hydroxide.

NDC 68012-154-30 Bottles of 30 chewable tablets

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]. Do not store this product at temperatures above 30°C (86°F).

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

17 PATIENT COUNSELING INFORMATION

Instruct patients to take ZEGERID with Magnesium Hydroxide chewable tablets on an empty stomach at least one hour prior to a meal. *[See Dosage and Administration (2)]*

PATIENTS SHOULD BE INSTRUCTED TO CHEW THE TABLET AND SWALLOW WITH WATER. DO NOT USE OTHER LIQUIDS.

PATIENTS SHOULD BE INSTRUCTED TO NOT SUBSTITUTE ZEGERID WITH MAGNESIUM HYDROXIDE CHEWABLE TABLETS FOR OTHER ZEGERID DOSAGE FORMS because different dosage forms contain different amounts of sodium bicarbonate and magnesium hydroxide. *[See Dosage and Administration (2)]*

ZEGERID with Magnesium Hydroxide chewable tablets are available in 40 mg and 20 mg dosage strengths of omeprazole with 600 mg sodium bicarbonate plus 700 mg magnesium hydroxide per tablet.

Patients should be instructed to not substitute two 20 mg chewable tablets for one 40 mg chewable tablet because the 20 mg and 40 mg chewable tablets contain the same amount of sodium bicarbonate (600 mg) and magnesium hydroxide (700 mg). Substituting two 20 mg chewable tablets for one 40 mg chewable tablet would result in the patient receiving twice as much sodium bicarbonate and magnesium hydroxide. Conversely patients should not substitute ½ of a 40mg chewable tablet for a 20mg chewable tablet.*[See Dosage and Administration (2)]*

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)]*

Patients on a sodium-restricted diet or patients at risk of developing congestive heart failure (CHF) should be informed of the sodium content of ZEGERID with Magnesium Hydroxide chewable tablets. 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 ZEGERID with Magnesium Hydroxide chewable tablets include headache, abdominal pain, nausea, diarrhea, vomiting and flatulence. *[See Adverse Reactions (6)]*

Pregnant women should be advised that a harmful effect of ZEGERID with Magnesium Hydroxide chewable 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)]*

SANTARIS INC.®

ZEGERID® with Magnesium Hydroxide Chewable Tablets are manufactured for Santarus, Inc., San Diego, CA 92130 by: Patheon Pharmaceuticals, Inc. Cincinnati, OH 45237

For more information call 1-888-778-0887

ZEGERID® is a registered trademark of Santarus, Inc.

This product is covered by one or more of the following: U.S. Patent Nos. 5,840,737; 6,489,346; 6,699,885; 6,780,882; 6,645,988, and 7,399,772 and additional patents pending.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEGERID (omeprazole/sodium bicarbonate) **Powder for Oral Suspension and Capsules safely and effectively. See full prescribing information for ZEGERID Powder for Oral Suspension and Capsules.**

ZEGERID (omeprazole/sodium bicarbonate) Powder for Oral Suspension and Capsules
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
ZEGERID Powder for Oral Suspension and Capsules is a proton pump inhibitor indicated for:

- Short-term treatment of active duodenal ulcer (1.1)
- Short-term treatment of active benign gastric ulcer (1.2)
- Treatment of gastroesophageal reflux disease (GERD) (1.3)
- Maintenance of healing of erosive esophagitis (1.4)
- Reduction of risk of upper GI bleeding in critically ill patients (1.5)

The safety and effectiveness of ZEGERID Powder for Oral Suspension and Capsules in pediatric patients (<18 years of age) have not been established. (8.3)

----------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)) (2)
- Gastric Ulcer: 40 mg once daily for 4-8 weeks (2)
- Gastroesophageal Reflux Disease (GERD) (2.)
  - 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)
- Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients: (40mg oral suspension only) 40 mg initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days

----------DOSAGE FORMS AND STRENGTHS----------

- ZEGERID (omeprazole/sodium bicarbonate) is available as a capsule and as a powder for oral suspension in 20 mg and 40 mg strengths (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to any components of the formulation (4)

----------WARNINGS AND PRECAUTIONS----------

- Concomitant Gastric Malignancy: Symptomatic response to therapy with ZEGERID Powder for Oral Suspension and Capsules 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 (5.3):
  Sodium content to be taken into consideration when administering to patients on a sodium-restricted diet
  To be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance because of its sodium bicarbonate content; long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 2%) are:
Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence (6)

To report SUSPECTED ADVERSE REACTIONS, contact Santarus Inc. at 1-888-778-0887, option 2 or http://www.santarus.com/contact/, 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): ZEGERID can prolong their elimination. Monitor to determine the need for possible dose adjustments when taken with ZEGERID (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): ZEGERID may interfere with absorption due to inhibition of gastric acid secretion (7)
- Voriconazole: May increase plasma levels of omeprazole (7)
- ZEGERID may reduce plasma levels of atazanavir and nelfinavir (7)
- ZEGERID may increase serum levels of tacrolimus, voriconazole, saquinavir, and clarithromycin (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based upon animal data, may cause fetal harm (8.1)
- The safety and effectiveness of ZEGERID in pediatric patients less than18 years of age have not been established. (8.4)
- Hepatic Impairment: Consider dose reduction, particularly for maintenance of healing of erosive esophagitis (12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: January 2010

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Duodenal Ulcer

ZEGERID (omeprazole/sodium bicarbonate) 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

ZEGERID 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
ZEGERID is indicated for the treatment of heartburn and other symptoms associated with GERD. *[See Clinical Studies (14.3)]*

Erosive Esophagitis
ZEGERID is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

The efficacy of ZEGERID 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 ZEGERID may be considered. *[See Clinical Studies (14.3)]*

1.4 Maintenance of Healing of Erosive Esophagitis

ZEGERID is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months. *[See Clinical Studies (14.4)]*

1.5 Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40mg oral suspension only)

ZEGERID Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients. [See **CLINICAL STUDIES**, Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (14.5)]

2 DOSAGE AND ADMINISTRATION

ZEGERID (omeprazole/sodium bicarbonate) is available as a capsule and as a powder for oral suspension in 20 mg and 40 mg strengths of omeprazole for adult use. Directions for use for each indication are summarized in Table 1. All recommended doses throughout the labeling are based upon omeprazole

Since both the 20 mg and 40 mg **oral suspension** packets contain the same amount of sodium bicarbonate (1680 mg), two packets of 20 mg are **not** equivalent to one packet of ZEGERID 40 mg; therefore, two 20 mg packets of ZEGERID should not be substituted for one packet of ZEGERID 40 mg.

Since both the 20 mg and 40 mg **capsules** contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are **not** equivalent to one capsule of ZEGERID 40 mg; therefore, two 20 mg capsules of ZEGERID should not be substituted for one capsule of ZEGERID 40 mg.

ZEGERID should be taken on an empty stomach at least one hour before a meal.

For patients receiving continuous Nasogastric (NG)/ Orogastric (OG) tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of ZEGERID Powder for Oral Suspension.

Table 1: Recommended Doses of ZEGERID by Indication for Adults 18 Years and Older

Indication	Recommended Dose	Frequency
Short-Term Treatment of Active Duodenal Ulcer	20 mg	Once daily for 4 weeks*,+
Benign Gastric Ulcer	40 mg	Once daily for 4-8 weeks **,+
Gastroesophageal Reflux Disease (GERD)		
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**
Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg oral suspension only)	40 mg	40 mg initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days**

* Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy. *[See Clinical Studies (14.1)]*
** For additional information, *[See Clinical Studies (14)]*
+ For additional information, *[See Indications and Usage (1)]*section

Special Populations

Hepatic Insufficiency
Consider dose reduction, particularly for maintenance of healing of erosive esophagitis. *[See Clinical Pharmacology (12.3)]*

Administration of Capsules

ZEGERID Capsules should be swallowed intact with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Preparation and Administration of Suspension

Directions for use: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

If ZEGERID is to be administered through a nasogastric (NG) or orogastric (OG) tube, the suspension should be constituted with approximately 20 mL of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and administer immediately. An appropriately-sized syringe should be used to instill the suspension in the tube. The suspension should be washed through the tube with 20 mL of water.

3 DOSAGE FORMS AND STRENGTHS

ZEGERID 20-mg Capsules: Each opaque, hard gelatin, white capsule, imprinted with the Santarus logo and “20”, contains 20 mg omeprazole and 1100 mg sodium bicarbonate.

ZEGERID 40-mg Capsules: Each opaque, hard gelatin, colored dark blue and white capsule, imprinted with the Santarus logo and “40”, contains 40 mg omeprazole and 1100 mg sodium bicarbonate.

ZEGERID Powder for Oral Suspension is a white, flavored powder packaged in unit-dose packets. Each packet contains either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate.

4 CONTRAINDICATIONS

ZEGERID 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.

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 ZEGERID Capsule contains 1100 mg (13 mEq) of sodium bicarbonate. The total content of sodium in each capsule is 304 mg.

Each packet of ZEGERID Powder for Oral Suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+).

The sodium content of ZEGERID products should be taken into consideration when administering to patients on a sodium restricted diet.

Because ZEGERID products contain sodium bicarbonate, they should be used with caution in patients with Bartter's syndrome, hypokalemia, hypocalcemia, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

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

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 2 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 2: Adverse Reactions Occurring In 1% or More of Patients on Omeprazole Therapy

	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 (1.6)	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

Table 3 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2,631 patients and subjects received omeprazole.

Table 3: Incidence of Adverse Reactions ≥ 1% Causal Relationship not Assessed

	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

A controlled clinical trial was conducted in 359 critically ill patients, comparing ZEGERID 40 mg/1680 mg suspension once daily to I.V. cimetidine 1200 mg/day for up to 14 days. The incidence and total number of AEs experienced by ≥ 3% of patients in either group are presented in Table 4 by body system and preferred term.

Table 4: Number (%) of Critically Ill Patient with Frequently Occurring (≥ 3%) Adverse Events by Body System and Preferred Term

MedDRA Body System / Preferred Term	ZEGERID® (N=178) All AEs n (%)	Cimetidine (N=181) All AEs n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia NOS	14 (7.9)	14 (7.7)
Anemia NOS Aggravated	4 (2.2)	7 (3.9)
Thrombocytopenia	18 (10.1)	11 (6.1)
CARDIAC DISORDERS		
Atrial Fibrillation	11 (6.2)	7 (3.9)
Bradycardia NOS	7 (3.9)	5 (2.8)
Supraventricular Tachycardia	6 (3.4)	2 (1.1)
Tachycardia NOS	6 (3.4)	6 (3.3)
Ventricular Tachycardia	8 (4.5)	6 (3.3)
GASTROINTESTINAL DISORDERS *		
Constipation	8 (4.5)	8 (4.4)
Diarrhea NOS	7 (3.9)	15 (8.3)
Gastric Hypomotility	3 (1.7)	6 (3.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Hyperpyrexia	8 (4.5)	3 (1.7)
Edema NOS	5 (2.8)	11 (6.1)
Pyrexia	36 (20.2)	29 (16.0)
INFECTIONS AND INFESTATIONS		
Candidal Infection NOS	3 (1.7)	7 (3.9)
Oral Candidiasis	7 (3.9)	1 (0.6)
Sepsis NOS	9 (5.1)	9 (5.0)
Urinary Tract Infection NOS	4 (2.2)	6 (3.3)
INVESTIGATIONS		
Liver Function Tests NOS Abnormal	3 (1.7)	6 (3.3)
METABOLISM AND NUTRITION DISORDERS		
Fluid Overload	9 (5.1)	14 (7.7)
Hyperglycaemia NOS	19 (10.7)	21 (11.6)
Hyperkalaemia	4 (2.2)	6 (3.3)
Hypernatraemia	3 (1.7)	9 (5.0)
Hypocalcaemia	11 (6.2)	10 (5.5)
Hypoglycaemia NOS	6 (3.4)	8 (4.4)
Hypokalaemia	22 (12.4)	24 (13.3)
Hypomagnesaemia	18 (10.1)	18 (9.9)
Hyponatraemia	7 (3.9)	5 (2.8)
Hypophosphataemia	11 (6.2)	7 (3.9)
PSYCHIATRIC DISORDERS		
Agitation	6 (3.4)	16 (8.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Acute Respiratory Distress Syndrome	6 (3.4)	7 (3.9)
Nosocomial Pneumonia	20 (11.2)	17 (9.4)
Pneumothorax NOS	1 (0.6)	8 (4.4)
Respiratory Failure	3 (1.7)	6 (3.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Decubitus Ulcer	6 (3.4)	5 (2.8)
Rash NOS	10 (5.6)	11 (6.1)
VASCULAR DISORDERS		
Hypertension NOS	14 (7.9)	6 (3.3)
Hypotension NOS	17 (9.6)	12 (6.6)

* Clinically significant upper gastrointestinal bleeding was considered a serious adverse event but it is not included in this table.

NOS = Not otherwise specified.

6.2 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

Cardiovascular
Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal
Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. 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 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
Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional
Hyponatremia, hypoglycemia, and weight gain.

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

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

Respiratory
Epistaxis, pharyngeal pain.

Skin
Severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema , pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.

Special Senses
Tinnitus, taste perversion.

Ocular
Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

Urogenital
Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

Hematologic
Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate include metabolic alkalosis, seizures, and tetany.

7 DRUG INTERACTIONS

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, and iron salts). In the clinical efficacy trials, antacids were used concomitantly with the administration of omeprazole.

Drugs metabolized by cytrochrom 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 P-450 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 ZEGERID.

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 Cmax 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.

Antiretroviral Agents
Concomitant administration 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 reduct 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%, Cmax by 37% and 89% and Cmin 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%, Cmax by 96%, and Cmin 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 Cmax by 75% and in Cmin 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.

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 (Cmax, AUC0-24, and T1/2 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-hydroxyclarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean Cmax was 10% greater, the mean Cmin 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-hydroxyclarithromycin, the mean Cmax was 45% greater, the mean Cmin 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 Dose[1]

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

[1]Mean ± (µg/g)

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, eg, 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.

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-lethality, 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 Animal Toxicology and/or Pharmacology (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, ZEGERID 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 should be used with caution in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of ZEGERID have not been established in pediatric patients less than 18 years of age.

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 ZEGERID. 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. *[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.

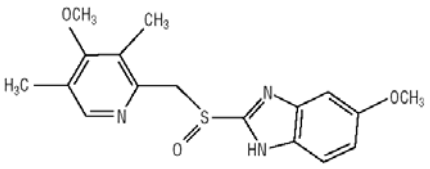
As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local 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.

11 DESCRIPTION

ZEGERID® (omeprazole/sodium bicarbonate) is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate, an antacid. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



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.

ZEGERID is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and sodium stearyl fumarate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

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. ZEGERID Capsules and Powder for Oral Suspension are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

12.2 Pharmacodynamics

Antisecretory Activity
Results from a PK/PD study of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of ZEGERID Oral Suspension in healthy subjects are shown in Table 5 below.

Table 5: Effect of ZEGERID Oral Suspension on Intragastric pH, Day 7

	Omeprazole/Sodium Bicarbonate	
Parameter	**40 mg/1680 mg (n = 24)**	**20 mg/1680 mg (n = 28)**
% Decrease from Baseline for Integrated Gastric Acidity (mmol·hr/L)	84%	82%
Coefficient of variation	20%	24%
% Time Gastric pH > 4* (Hours)*	77% (18.6 h)	51% (12.2 h)
Coefficient of variation	27%	43%
Median pH	5.2	4.2
Coefficient of variation	17%	37%

Note: Values represent medians. All parameters were measured over a 24-hour period.
* $p < 0.05$ 20 mg vs. 40 mg

Results from a separate PK/PD study of antisecretory effect on repeated once-daily dosing of 40 mg/1100 mg and 20 mg/1100 mg of ZEGERID Capsules in healthy subjects show similar effects in general on the above three PD parameters as those for ZEGERID 40 mg/1680 mg and 20 mg/1680 mg Oral Suspension, respectively.

The antisecretory effect lasts longer than would be expected from the very 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 vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

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

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

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

12.3 Pharmacokinetics

Absorption
In separate *in vivo* bioavailability studies, when ZEGERID Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of ZEGERID Powder for Oral Suspension (compared to I.V. administration) is about 30-40% at doses of 20 – 40 mg, due in large part to presystemic metabolism.

When ZEGERID Oral Suspension 40 mg/1680 mg was administered in a two-dose loading regimen, the omeprazole AUC (0-inf) (ng·hr/mL) was 1665 after Dose 1 and 3356 after Dose 2, while Tmax was approximately 30 minutes for both Dose 1 and Dose 2.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from ZEGERID are approximately proportional from 20 to 40 mg doses, 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 ZEGERID is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% 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 3.2 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, similar to that of young healthy subjects.

Pediatric
The pharmacokinetics of ZEGERID 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 I.V. 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 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 m^2, 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.

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 H_2-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 omeprazole 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 138.0 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 ($p \leq 0.01$). (See Table 6)

Table 6: 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

* ($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$). (See Table 7)

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

	Omeprazole 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d. (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 b.i.d. ($p < 0.01$).

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 b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs. (See Table 8)

Table 8: Treatment of Active Duodenal Ulcer % of Patients Healed

	Omeprazole 40 mg (n = 36)	Omeprazole 20 mg (n = 34)	Ranitidine 150 mg b.i.d. (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. (See Table 9)

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

	Omeprazole 40 mg q.d. (n = 214)	Omeprazole 20 mg q.d. (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. (See Table 10)

Table 10: Treatment of Gastric Ulcer % of Patients Healed (All Patients Treated)

	Omeprazole 40 mg q.d. (n = 187)	Omeprazole 20 mg q.d. (n = 200)	Ranitidine 150 mg b.i.d. (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. Results are shown in Table 11.

Table 11: % 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 delayed release capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as shown in Table 12.

Table 12: % 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 13.

Table 13: Life Table Analysis

	Omeprazole 20 mg q.d. (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. Table 14 provides the results of this study for maintenance of healing of erosive esophagitis.

Table 14: Life Table Analysis

	Omeprazole 20 mg q.d. (n = 131)	Omeprazole 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	77*	58‡	46

* ($p = 0.01$) Omeprazole 20 mg once daily versus Omeprazole 10 mg once daily or Ranitidine.
‡ ($p = 0.03$) Omeprazole 10 mg once daily versus Ranitidine.

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

14.5 Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

A double-blind, multicenter, randomized, non-inferiority clinical trial was conducted to compare ZEGERID Oral Suspension 40 mg/1680 mg and I.V. cimetidine for the reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients (mean APACHE II score = 23.7). The primary endpoint was significant upper GI bleeding defined as bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, or persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage. ZEGERID Oral Suspension 40 mg/1680 mg (two doses administered 6 to 8 hours apart on the first day via orogastric or nasogastric tube, followed by 40 mg q.d. thereafter) was compared to continuous I.V. cimetidine (300 mg bolus, and 50 to 100 mg/hr continuously thereafter) for up to 14 days (mean = 6.8 days). A total of 359 patients were studied, age range 16 to 91 (mean = 56 yrs), 58.5% were males, and 64% were Caucasians. The results of the study showed that ZEGERID was non-inferior to I.V. cimetidine, 10/181(5.5%) patients in the cimetidine group vs. 7/178 (3.9%) patients in the ZEGERID group experienced clinically significant upper GI bleeding.

15 REFERENCES

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3. Ruigómez A, Rodriquez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; 150: 476-81
4. 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

ZEGERID 20-mg Capsules: Each opaque, hard gelatin, white capsule, imprinted with the Santarus logo and "20", contains 20 mg omeprazole and 1100 mg sodium bicarbonate.

NDC 68012-102-30 Bottles of 30 capsules

ZEGERID 40-mg Capsules: Each opaque, hard gelatin, colored dark blue and white capsule, imprinted with the Santarus logo and "40", contains 40 mg omeprazole and 1100 mg sodium bicarbonate.

NDC 68012-104-30 Bottles of 30 capsules

ZEGERID Powder for Oral Suspension is a white, flavored powder packaged in unit-dose packets. Each packet contains either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate.

NDC 68012-052-30 Cartons of 30: 20-mg unit-dose packets
NDC 68012-054-30 Cartons of 30: 40-mg unit-dose packets

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

Instruct patients that ZEGERID should be taken on an empty stomach at least one hour prior to a meal. *[See Dosage and Administration (2)]*

Instruct patients in Directions for Use as follows:

Capsules: Swallow intact capsule with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

ZEGERID is available either as 40 mg or 20 mg capsules with 1100 mg sodium bicarbonate. ZEGERID is also available either as 40 mg or 20 mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

Patients should be instructed not to substitute Zegerid Capsules or Suspension for other ZEGERID dosage forms because different dosage forms contain different amounts of sodium bicarbonate and magnesium hydroxide. *[See Dosage and Administration (2)]*

Patients should be advised that since both the 20 mg and 40 mg **oral suspension** packets contain the same amount of sodium bicarbonate (1680 mg), two packets of 20 mg are **not** equivalent to one packet of ZEGERID 40 mg; therefore, two 20 mg packets of ZEGERID should not be substituted for one packet of ZEGERID 40 mg. Conversely ½ of a 40mg packet should not be substituted for one 20mg packet. *[See Dosage and Administration (2)]*

Patients should be advised that since both the 20 mg and 40 mg **capsules** contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are **not** equivalent to one capsule of ZEGERID 40 mg; therefore, two 20 mg capsules of ZEGERID should not be substituted for one capsule of ZEGERID 40 mg. *[See Dosage and Administration (2)]*

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)]*

Patients on a sodium-restricted diet or patients at risk of developing congestive heart failure (CHF) should be informed of the sodium content of ZEGERID Capsules (304 mg per tablet) and ZEGERID Powder (460 mg per

packet). 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 ZEGERID include headache, abdominal pain, nausea, diarrhea, vomiting and flatulence. *[See Adverse Reactions (6)]*

Pregnant women should be advised that a harmful effect of ZEGERID 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)]*

ZEGERID® Capsules are manufactured for Santarus, Inc., San Diego, CA 92130 by Norwich Pharmaceuticals, Inc., North Norwich, NY 13814.

ZEGERID® Powder for Oral Suspension is manufactured for Santarus, Inc. by Patheon Inc., Whitby, Ontario L1N 5Z5, Canada.

For more information call 1-888-778-0887

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This product is covered by one or more of the following: U.S. Patent Nos. 5,840,737; 6,489,346; 6,699,885; 6,780,882; 6,645,988, and 7,399,772 and additional patents pending.

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