OMEPRAZOLE (Systemic)

Category

Gastric acid pump inhibitor; antiulcer agent 1.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Dyspepsia (treatment)¾Omeprazole is indicated for the treatment of a complex of symptoms which may be caused by any of the conditions where a reduction in gastric acid secretion is required (e.g., duodenal ulcer, gastric ulcer, nonsteroidal anti-inflammatory drugs [NSAID]-associated gastric and duodenal ulcer, reflux esophagitis, gastroesophageal reflux disease [GERD])or when no identifiable organic cause is found (i.e., functional dyspepsia) 49, 50

Gastroesophageal reflux disease [GERD] (prophylaxis and treatment) ¾Omeprazole is indicated for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease 43.

Omeprazole is indicated for the short-term treatment of erosive esophagitis (associated with GERD) that has been diagnosed by endoscopy 43.

Omeprazole also is indicated to maintain healing of erosive esophagitis. 38, 39, 43

Hypersecretory conditions, gastric (treatment) 43

Zollinger-Ellison syndrome (treatment) 30, 34, 42, 43

Mastocytosis, systemic (treatment) 43 or

Adenoma, multiple endocrine (treatment) 43¾Omeprazole is indicated for the long-term treatment of pathologic gastric hypersecretion associated with Zollinger-Ellison syndrome (alone or as part of multiple endocrine neoplasia Type-1) 27 , systemic mastocytosis, and multiple endocrine adenoma. 1

Ulcer, peptic (treatment)¾Omeprazole is indicated for the short-term treatment of active duodenal ulcer 1, 26, 31 and active benign gastric ulcer 26, 32, 41.

Ulcer, peptic, Helicobacter pylori -associated (treatment adjunct)¾Omeprazole is indicated in combination with clarithromycin [and amoxicillin or metronidazole 42] for the treatment of duodenal and gastric ulcer associated with H. pylori infection 42, 43.

Eradication of H. pylori has been shown to reduce the risk of ulcer recurrence 43.

[Ulcer, peptic, nonsteroidal anti-inflammatory drug-induced (treatment)]¾Omeprazole is indicated for the treatment of duodenal or gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). 42

Precautions to Consider

Carcinogenicity/Tumorigenicity/Mutagenicity

In two 2-year studies in rats, omeprazole, given in doses corresponding to 4 to 352 times the human dose, caused end-life gastric carcinoid tumors and enterochromaffin-like (ECL) cell hyperplasia in a dose-related manner in both male and female animals. 1, 46 Incidence was markedly higher in female rats, which had higher blood levels of omeprazole 46.

These ECL cell changes have been shown to be caused by high levels of gastrin (or hypergastrinemia) 27.

Pronounced acid inhibition at extremely high doses of gastric acid pump inhibitors or H 2-receptor antagonists results in the same feedback elevation of gastrin and subsequent ECL cell changes of the stomach. 27

Omeprazole was not mutagenic in the Ames test, in an in vitro mouse lymphoma cell assay, and in an in vivo rat liver DNA damage assay. 46 A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an in vivo bone marrow chromosome aberration test. A second mouse micronucleus test at 2000 times the human dose, but with different (suboptimal) sampling times, was negative 46.

Pregnancy/Reproduction

Fertility¾In a rat fertility and general reproductive performance test, omeprazole, in a dose 35 to 345 times the human dose, was not toxic or deleterious to the reproductive performance of parental animals. 1, 46

Pregnancy¾Adequate and well-controlled studies in humans have not been done 46.

Sporadic instances of congenital abnormalities in infants born to women who received omeprazole during pregnancy have been reported. 46

Studies in pregnant rats did not show omeprazole to have any teratogenic potential at doses 345 times the human dose. Omeprazole produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions in rabbits receiving 17 to 172 times the human dose. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with 35 to 345 times the human dose. 1

FDA Pregnancy Category C. 1

Breast-feeding

It is not known whether omeprazole is distributed into human milk. However, because omeprazole has been shown to cause tumorigenic and carcinogenic effects in animals, risk-benefit must be considered. 1, 46

Pediatrics

Appropriate studies on the relationship of age to the effects of omeprazole have not been performed in the pediatric population. 1 Safety and efficacy have not been established 46.

Geriatrics

No information is available on the relationship of age to the effects of omeprazole in geriatric patients. However, a somewhat decreased rate of elimination and an increased bioavailability are more likely to occur in geriatric patients taking omeprazole. 1

Pharmacogenetics

Pharmacokinetic studies in Asian subjects receiving single 20-mg doses of omeprazole showed an approximately fourfold increase in the area under the plasma concentration-time curve (AUC) as compared to Caucasian subjects. 38, 39 Dosage adjustments should be considered for Asian patients, especially for prophylaxis of recurrence of erosive esophagitis. 38, 39

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Only specific interactions between omeprazole and other medications have been identified in this monograph. However, omeprazole, by increasing gastric pH, has the potential to affect the bioavailability of any medication for which absorption is pH-dependent. Also, omeprazole may prevent the degradation of acid-labile drugs. 10

In addition, because of omeprazole's ability to inhibit hepatic microsomal drug metabolism, elimination of other medications that require hepatic metabolism via the cytochrome P450 system or that are highly extracted by the liver may be decreased during concurrent use with omeprazole. 14

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Ampicillin esters 1, 46

Iron salts 1, 46 or

Itraconazole 47 or

Ketoconazole 1, 18, 46, 47

(omeprazole may increase gastrointestinal pH; concurrent use with omeprazole may result in a reduction in absorption of ampicillin esters, iron salts, itraconazole, or ketoconazole) 1, 18

>> Anticoagulants, coumarin- or indandione-derivative or 37, 46, 47, 48

>> Diazepam or 18, 28, 29, 40, 46, 47, 48

>> Phenytoin 18, 40, 46, 47, 48

(inhibition of the cytochrome P450 enzyme system by omeprazole, especially in high doses, may cause a decrease in the hepatic metabolism of these medications, which may result in delayed elimination and increased blood concentrations, when these medications are used concurrently with omeprazole 1, 14)
(monitoring of blood concentrations, or prothrombin time for anticoagulants, is recommended as a guide to dosage since dosage adjustment of these medications may be necessary during and after omeprazole therapy to prevent bleeding due to anticoagulant potentiation 1, 18)

Bone marrow depressants 1 (see Appendix II)

(concurrent use of omeprazole with these medications may increase the leukopenic and/or thrombocytopenic effects of both these medications; if concurrent use is required, close observation for toxic effects should be considered 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1, 16, 18, 19, 46 and

Alkaline phosphatase 1, 18, 46, 19 and

Aspartate aminotransferase (AST [SGOT]) 1, 18, 19, 46

(serum values may be increased)

Gastrin, serum 47, 48

(concentrations will increase during the first 1 to 2 weeks of omeprazole therapy and return to normal after the medication is discontinued; this increase is probably due to the inhibition of acid secretion, which eliminates the negative feedback effect of acid on gastrin secretion; in addition to stimulating gastric acid secretion, gastrin promotes the growth and proliferation of endocrine or enterochromaffin-like [ECL] cells in the gastric mucosa 1, 18, 22)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Hepatic disease, chronic, current or history of

(dosage reduction may be required due to increased half-life in chronic hepatic disease 1)

Sensitivity to omeprazole 46

Side/Adverse Effects

Note: Gastric fundic gland polyps have occurred rarely in patients receiving omeprazole; these appear to be benign and reversible upon discontinuance of omeprazole. 38, 39, 46

Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome who have received long-term omeprazole therapy. These carcinoids are believed to be a manifestation of the underlying syndrome, which is known to be associated with such tumors. 38, 39, 46

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patient receiving long-term omeprazole therapy. 38, 39, 46

Overt liver disease has occurred rarely, and included hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (sometimes fatal), hepatic failure (sometimes fatal), and hepatic encephalopathy. 46

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Generalized skin reactions, including toxic epidermal necrolysis 46 (blisters; chills; fever; general feeling of discomfort or illness; muscle aches; red or irritated eyes; redness, tenderness, itching, burning, or peeling of skin; sore throat; sores or ulcers on lips or in mouth)¾sometimes fatal; Stevens-Johnson syndrome 46 (bleeding or crusting sores on lips; chills; fever; muscle cramps; pain; skin rash or itching; sore throat; sores, ulcers, or white spots on lips, in mouth, or on genitals); or erythema multiforme 46 (blisters on palms of hands and soles of feet; fever; general feeling of discomfort or illness; joint pain; redness of skin); hematologic abnormalities, specifically anemia 1, 23, 46 (unusual tiredness or weakness); agranulocytosis 46 (chills; fever; sore throat; unusual tiredness or weakness)¾sometimes fatal; hemolytic anemia 46 (back, leg, or stomach pain; loss of appetite; unusual tiredness or weakness); leukocytosis 1, 23, 46 (sore throat and fever); neutropenia 1, 46 (continuing ulcers or sores in mouth); pancytopenia 1, 46 or thrombocytopenia 1 (unusual bleeding or bruising); hematuria 1 (bloody urine); proteinuria 1 (cloudy urine); urinary tract infection 1 (bloody or cloudy urine; difficult, burning, or painful urination; frequent urge to urinate)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain or colic 1, 7, 18, 46, 47
Incidence less frequent

Asthenia 1, 46 (muscle pain; unusual tiredness); back pain 46; central nervous system (CNS) disturbances 1 , specifically dizziness 1, 18, 46, 47; headache 1, 46, 47, 48; somnolence 1, 18 (unusual drowsiness); or unusual tiredness 1, 18; chest pain 1; gastrointestinal disturbances, specifically acid regurgitation 1, 18, 46 (heartburn); constipation 1, 18, 46, 47; diarrhea or loose stools 1, 18, 36, 46, 47, 48; flatulence 1, 46 (gas); or nausea and vomiting 1, 18, 46, 47; skin rash or itching 1, 18, 25, 36, 46, 47

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Blurred vision 41, 46; confusion 41, 44, 46; diaphoresis 41, 46 (increased sweating); drowsiness 41, 44, 46; dryness of mouth 41, 46; flushing 41, 44, 46; headache 41, 44, 46; malaise 44 (general feeling of discomfort or illness); nausea 41, 46; tachycardia 41, 44, 46 (fast or irregular heartbeat)
Treatment of overdose

Since there is no specific antidote for overdose with omeprazole, treatment should be symptomatic and supportive. 1, 41, 46 Due to extensive protein binding, omeprazole is not readily dialyzable. 41, 46 Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Omeprazole (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to omeprazole
Pregnancy¾Reports of congenital defects; risk-benefit must be considered
Breast-feeding¾May be distributed into breast milk; may cause potentially serious adverse effects in nursing infants
Other medications, especially anticoagulants, diazepam, or phenytoin
Other medical problems, especially chronic hepatic disease or history of
Proper use of this medication

Taking the capsule form of this medication immediately before a meal, preferably the morning meal

May take antacids for relief of pain, unless otherwise instructed by physician

Swallowing capsule form of this medication whole; not crushing, breaking, chewing, or opening the capsule

>> Compliance with full course of therapy

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress

Side/adverse effects

Signs of potential side effects, especially generalized skin reactions, hematologic abnormalities, hematuria, proteinuria, and urinary tract infection

General Dosing Information

Omeprazole capsules should be swallowed whole, and not chewed or crushed. 46 Omeprazole magnesium tablets also should be swallowed whole 42.

Symptomatic response to omeprazole therapy does not preclude the presence of gastric malignancy 46.

For therapy of dyspepsia, omeprazole usually is used for 4 weeks. If after 2 weeks of treatment the patient does not respond to therapy, or there is an early clinical indication of a lack of efficacy, the patient should be thoroughly investigated in order to rule out organic disease. If there are indications of a clinical response following the initial 2 weeks of treatment, omeprazole may be continued for an additional 2 weeks. 49, 50

For therapy of gastrointestinal reflux disease, omeprazole usually is used for short-term (4- to 8-week) courses; however, additional 4- to 8-week courses of treatment may be considered if there is recurrence of severe or symptomatic gastroesophageal reflux poorly responsive to customary medical treatment. 38, 39 Controlled studies of omeprazole used as maintenance therapy to prevent erosive esophagitis recurrence have not been conducted beyond 12 months 38, 39, 40 , although a limited number of patients have received continuous maintenance treatment for up to 6 years. 40 Dosage adjustments should be considered for Asian patients, especially for prophylaxis of erosive esophagitis recurrence 38, 39 , since pharmacokinetic studies in Asian subjects receiving single 20-mg doses of omeprazole showed an approximately fourfold increase in the area under the plasma concentration-time curve (AUC) as compared to Caucasian subjects. 38, 39

Omeprazole may be taken with antacids. 27, 46, 47

Initial titration of doses and subsequent dosage adjustment of omeprazole is recommended in the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas). Doses of up to 120 mg three times a day have been

administered. 41 Patients may require at least one increase in dose per year. If the daily dose is greater than 80 mg, it should be administered in divided doses. 41 Zollinger-Ellison syndrome has been treated continuously with omeprazole for more than 5 years. 1, 41

Diet/Nutrition

Omeprazole capsules should be taken immediately before meals 38, 39.

Omeprazole magnesium tablets may be taken with food or on an empty stomach. 40, 42, 43

Bioequivalence information

Omeprazole capsules and omeprazole magnesium tablets are not bioequivalent. 42

Oral Dosage Forms

Note: Dosing recommendations vary between dosage forms; please check the appropriate section for dosage form-specific dosing recommendations.

OMEPRAZOLE DELAYED-RELEASE CAPSULES

Usual adult dose

Gastroesophageal reflux disease (treatment) ¾
Oral, 20 mg once a day for four to eight weeks. 43

Note: A dosage of 40 mg once a day has been used for esophagitis associated with gastroesophageal reflux disease refractory to other treatment regimens. 26

Erosive esophagitis (prophylaxis)¾
Oral, 20 mg once a day. 38, 39, 43

Gastric hypersecretory conditions (e.g., Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas) ¾
Oral, 60 mg once a day, the dosage being adjusted as needed, and therapy continued for as long as clinically indicated. 1, 43 Doses of up to 120 mg three times a day have been used. 41, 43 If the total daily dose is greater than 80 mg, it should be administered in divided doses. 41, 43

Duodenal ulcer¾
Oral, 20 mg once a day. 1, 43

Note: The dosage can be increased to 40 mg once a day for duodenal ulcer refractory to other treatment regimens. 26

Gastric ulcer (treatment)¾
Oral, 40 mg once a day for four to eight weeks. 41, 43

Peptic ulcer associated with Helicobacter pylori infection¾

Oral, omeprazole 40 mg once a day before breakfast taken in combination with clarithromycin 500 mg three times a day for the first fourteen days 43.

For days 15 through 28, further treatment with omeprazole 20 mg once a day before breakfast follows 43.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾10 mg (Rx)[Prilosec]

20 mg (Rx)[Prilosec]

40 mg (Rx)[Prilosec]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light. 1

Auxiliary labeling:

· Take before meals.
· Swallow capsules whole.

OMEPRAZOLE MAGNESIUM DELAYED-RELEASE TABLETS

Note: The dosing and dosage forms of omeprazole magnesium are expressed in terms of omeprazole base.

Usual adult dose

Dyspepsia (treatment)¾
Oral, 20 mg once a day for four weeks. Some patients respond adequately to a dose of 10 mg once a day 49, 50.

Gastroesophageal reflux disease (treatment) ¾
Oral, 20 mg once a day for the relief of heartburn and regurgitation. 42, 50 Further investigation is needed if symptom control in not achieved after four weeks of treatment 50.

Some patients respond adequately to a dose of 10 mg once a day 42, 50.

In patients requiring maintenance therapy, doses of 10 mg once a day have been used 42, 50.

For the treatment of reflux esophagitis, 20 mg once a day is recommended 42, 50.

The dosage may be increased to 40 mg once a day for esophagitis refractory to other treatment regimens 26, 42, 50.

In patients requiring maintenance therapy, doses of 10 mg once a day have been used 42, 50.

If reflux esophagitis recurs, the dose may be increased to 20 or 40 mg once a day 42, 50.

Gastric hypersecretory conditions (e.g., Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas) ¾
Oral, 60 mg once a day, the dosage being adjusted as needed, and therapy continued for as long as clinically indicated. 42, 50 Doses of up to 120 mg three times a day have been used. 42, 50 If the total daily dose is greater than 80 mg, it should be administered in divided doses and given two times a day 50, 42.

Duodenal ulcer¾
Oral, 20 mg once a day. 42, 50 For patients not healed after the initial course of therapy (healing usually occurs within two weeks), an additional two weeks of treatment is needed. 50 The dosage may be increased to 20 to 40 mg once a day for duodenal ulcer refractory to other treatment regimens. 42, 50 In patients requiring maintenance therapy, doses of 10 mg once a day, increased to 20 to 40 mg once a day as needed, have been used. 42, 50

Gastric ulcer (treatment)¾
Oral, 20 mg once a day. 42, 50 For patients not healed after the initial course of therapy (healing usually occurs within four weeks), an additional four weeks of treatment is needed. 50 The dosage may be increased to 40 mg once a day for gastric ulcer refractory to other treatment regimens 42, 50.

In patients requiring maintenance therapy, doses of 20 mg once a day, increased to 40 mg once a day as needed, have been used 42, 50.

Peptic ulcer associated with H. pylori infection¾
Oral, triple therapy regimens of omeprazole 20 mg, plus clarithromycin 500 mg, plus amoxicillin 1000 mg or omeprazole 20 mg, plus clarithromycin 250 mg, plus metronidazole 500 mg, in which all three medications are taken twice a day for seven days 42, 50.

These regimens are followed by further treatment with omeprazole, 20 mg once a day for up to three weeks for active duodenal ulcer, and 20 to 40 mg once a day for up to twelve weeks for active gastric ulcer 42, 50.

Peptic ulcer, nonsteroidal anti-inflammatory drug-induced (treatment)¾
Oral, 20 mg once a day 42, 50.

For patients not healed after the initial course of therapy (healing usually occurs within four weeks), an additional four weeks of treatment is needed 50.

In patients requiring maintenance therapy, doses of 20 mg once a day for up to six months have been used 42, 50.

Usual pediatric dose

Safety and efficacy have not been established.

Usual geriatric dose

See Usual adult dose.

The daily dose should not exceed 20 mg 50.

Strength(s) usually available
U.S.¾Not commercially available.
Canada¾10 mg (base) (Rx)[Losec]

20 mg (base) (Rx)[Losec]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from moisture and humidity.

Auxiliary labeling:

· Swallow tablets whole.

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