

PRODUCT MONOGRAPH

 **LOSEC[®]**

(omeprazole delayed release capsules)

10 and 20 mg omeprazole

H⁺, K⁺-ATPase Inhibitor

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PRODUCT MONOGRAPH

NAME OF DRUG

LOSEC®

(omeprazole delayed release capsules)

10 and 20 mg omeprazole

THERAPEUTIC CLASSIFICATION

H⁺, K⁺-ATPase Inhibitor

NOTE: When used in combination with amoxicillin, clarithromycin or metronidazole, the Product Monographs for those agents must be consulted and followed.

ACTIONS AND CLINICAL PHARMACOLOGY

LOSEC (omeprazole) inhibits the gastric enzyme H⁺,K⁺-ATPase (the proton pump) which catalyzes the exchange of H⁺ and K⁺. It is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose-dependent. Daily oral doses of omeprazole 20 mg and higher showed a consistent and effective acid control. A mean reduction of 24-hour intragastric acidity of approximately 80% was achieved during repeated dosing of 20 mg daily.

Treatment with LOSEC alone has been shown to suppress, but not eradicate *Helicobacter pylori* (*H. pylori*), a bacterium that is strongly associated with acid peptic disease. Approximately 90 to 100% of patients with duodenal ulcers, and 80% of patients with gastric ulcers, are infected with *H. pylori*. Clinical evidence indicates a synergistic effect between omeprazole and certain antibiotics in achieving eradication of *H. pylori*. Eradication of *H. pylori* is associated with symptom relief, healing of mucosal lesions, decreased rate of duodenal ulcer recurrence and long-term remission of peptic ulcer disease, reducing the need for prolonged antisecretory therapy.

There is no statistically significant change in the bioavailability (AUC, C_{max}) of amoxicillin during concomitant treatment with omeprazole in healthy volunteers.

There is an increase in the bioavailability (AUC) and half-life of omeprazole, and bioavailability (AUC) and C_{max} of clarithromycin, during concomitant administration in healthy volunteers.

There is no statistically significant change in the bioavailability (AUC, C_{max}) of metronidazole during concomitant treatment with omeprazole in healthy volunteers.

LOSEC is absorbed rapidly. After an initial oral dose of LOSEC, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. Peak plasma levels occur within about four hours.

The terminal plasma half-life is about 40 minutes. The antisecretory effect of omeprazole is directly proportional to the AUC; it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC, C_{max} and t_{max} . LOSEC 20 mg tablets demonstrate, after repeated dosing, increased plasma omeprazole AUC (18%) and maximum concentration (41%) in comparison to omeprazole 20 mg given as capsules.

The omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine. In contrast to the capsule, the tablet (as a single unit formulation) will enter the intestine and dissolve as one unit. Consequently, the absorption and first pass metabolism of the tablet take place only during a very limited period. This may be one of the reasons for the difference observed in the pharmacokinetic variables of the two formulations.

LOSEC 20 mg tablets and LOSEC 20 mg capsules have an equivalent pharmacodynamic effect assessed by the inhibition of stimulated acid secretion and effect on 24-hour intragastric pH.

Omeprazole undergoes first-pass metabolism by the cytochrome P-450 2C19 system, mainly in the liver. Following i.v. and oral administration, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces.

INDICATIONS AND CLINICAL USE

LOSEC (omeprazole) is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as

- duodenal ulcer;
- gastric ulcer;
- NSAID-associated gastric and duodenal ulcers;
- reflux esophagitis;
- symptomatic gastroesophageal reflux disease (GERD), *i.e.*, heartburn and regurgitation;
- Zollinger-Ellison syndrome (pathological hypersecretory condition);
- eradication of *Helicobacter pylori* (*H. pylori*)

LOSEC, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with peptic ulcer disease associated with *Helicobacter pylori* infection. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (*i.e.*, asymptomatic) remains to be determined.

Patients who fail to have their infection eradicated may be considered to have *H. pylori* resistant to the antimicrobials used in the eradication regimen. Therefore, therapy involving alternative effective antimicrobial agents should be considered (if re-treating).

It has been demonstrated that resistance to metronidazole is a negative predictive factor, decreasing the eradication rate of *H. pylori* obtained with triple therapy (omeprazole, metronidazole and clarithromycin) by 10-20%. The addition of omeprazole to metronidazole and clarithromycin appears to reduce the effect of primary resistance and the development of secondary resistance compared to antimicrobials alone.

Table 1 Results of studies in patients with a history of duodenal ulcer who were *H. pylori* -positive.

	Treatment	Eradication Rate	
		APT or ITT Analysis	PP Analysis
Study 1	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	96%	98%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	95%	94%
Study 2	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	94%	95%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	87%	91%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.

Study 1: Patients included in the APT and PP analyses were assessed for *H. pylori* status by UBT pre- and post-treatment, n = 684 (APT analysis).

Study 2: Patients included in the ITT and PP analyses were assessed for *H. pylori* status by UBT and culture pre- and post-treatment, n = 514 (ITT analysis).

Table 2 Results of studies in patients with active peptic ulcer who were *H. pylori* positive (ITT analysis).

	Treatment	Eradication Rate (PP Analysis)	Ulcer Healing Rate (Post Treatment)	Rate of Patients in Remission (6 months after cessation therapy)
Study 3	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	78% (87%)	92%	88%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	85% (92%)	94%	92%
Study 4	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	79% (83%)	94%	83%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	86% (93%)	96%	92%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.

Study 3: Patients with duodenal ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 146 (ITT analysis).

Study 4: Patients with gastric ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 145 (ITT analysis).

CONTRAINDICATIONS

Hypersensitivity to omeprazole or any of the components of this medication (see PHARMACEUTICAL INFORMATION).

WARNINGS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with LOSEC (omeprazole) is instituted, as treatment with LOSEC may alleviate symptoms and delay diagnosis.

Concomitant administration with atazanavir, nelfinavir or clopidogrel is not recommended (see PRECAUTIONS, Drug Interactions).

Use in Pregnancy

The safety of omeprazole in pregnancy has not been established. LOSEC should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers

It is not known if omeprazole is secreted in human milk. LOSEC should not be given to nursing mothers unless its use is considered essential.

Use in Children

The safety and effectiveness of LOSEC in children has not yet been established.

PRECAUTIONS

Use in the Elderly

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour). The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Insufficiency

Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours). Twenty mg given once daily to these patients for four weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Renal Insufficiency

The disposition of intact omeprazole is unchanged in patients with impaired renal function and no dose adjustment is needed in these patients (see DOSAGE AND ADMINISTRATION).

Carcinogenicity

The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life span during administration with 14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months' high-dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for seven years did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se (see TOXICOLOGY). Similar observations have been made after administration of histamine H₂-receptor blockers and also in partially fundectomized rats.

Short- and long-term treatment in a limited number of patients for up to six years has not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Drug Interactions

The absorption of some drugs might be altered due to decreased intragastric acidity. Thus, it can be predicted that the absorption of ketoconazole and itraconazole will decrease during

omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

Omeprazole is metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The pharmacokinetics of the following drugs which are also metabolized through the cytochrome P-450 system have been evaluated during concomitant use of omeprazole in humans: aminopyrine, antipyrine, clopidogrel, diazepam, phenytoin, warfarin (or other vitamin K antagonists), theophylline, voriconazole, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen.

Aminopyrine and Antipyrine

After 14 days' administration of 60 mg omeprazole once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days' administration of 30 mg once daily, no significant changes in clearance were noted.

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Co-administration of clopidogrel with omeprazole, an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel given concomitantly or 12 hours apart. Concomitant use of drugs that inhibit the activity of this enzyme may result in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

In a crossover clinical study, 72 healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study 72 healthy subjects were given the same doses of clopidogrel and omeprazole but the drugs were administered 12 hours apart; the results were similar indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction.

The pharmacological interaction between clopidogrel and omeprazole is related to partly shared metabolic pathways. Whether such an interaction translates into negative clinical outcomes is uncertain.

Diazepam, Phenytoin and Warfarin (or other vitamin K antagonists)

As LOSEC is metabolized through cytochrome P-450 2C19, it can alter the metabolism and prolong elimination of diazepam, warfarin (R-warfarin) and phenytoin.

Diazepam

Following repeated dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54%. The corresponding decrease after omeprazole 20 mg was 26%.

Warfarin (or other vitamin K antagonists)

Concomitant administration of omeprazole 20 mg in healthy subjects had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen. In patients receiving warfarin or other vitamin K antagonists, monitoring of INR (International Normalised Ratio) is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Phenytoin

Following three weeks' treatment with omeprazole 20 mg once daily, the steady-state plasma levels of phenytoin in epileptic patients already receiving concomitant phenytoin treatment were not significantly affected. Urinary excretion of phenytoin and its main metabolite were also unchanged.

After single intravenous and oral doses of omeprazole 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15-20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of phenytoin was increased by 27%. Thus, there appears to be a dose-dependent inhibition of elimination of phenytoin by omeprazole.

Patients receiving phenytoin and warfarin (or other vitamin K antagonists) should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole. Results from a range of interaction studies with LOSEC versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on any other clinically relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP 1A2 (caffeine, phenacetin, theophylline), CYP 2C9 (S-warfarin), CYP 2D6 (metoprolol, propranolol), CYP 2E1 (ethanol), and CYP 3A (cyclosporin, lidocaine, quinidine, estradiol).

Antiretroviral Drugs

Omeprazole, like other acid-reducing agents, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19.

Reports indicate that omeprazole has a significant impact on atazanavir exposure, decreasing AUC, C_{max} and C_{min} . This interaction is only partially overcome by the addition of ritonavir to the atazanavir treatment regimen. Similarly, decreased serum levels of nelfinavir have also been reported when given together with omeprazole. Concomitant administration of omeprazole with atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs where unchanged serum levels have been reported when given with omeprazole (see WARNINGS).

Tacrolimus

Although no clinical studies have been undertaken, there is a possibility that the concomitant administration of omeprazole and tacrolimus may increase serum levels of tacrolimus.

Theophylline

No effects on oral or i.v. theophylline kinetics have been observed after repeated once daily doses of 40 mg omeprazole.

Voriconazole

Concomitant administration of omeprazole and a CYP 2C19 and CYP 3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. However, a dose adjustment of omeprazole is not required.

Propranolol and Metoprolol

No effects on propranolol kinetics were observed in a steady-state trial with 20 mg of omeprazole daily. Similarly, no effects on steady state plasma levels of metoprolol were observed after concomitant treatment with 40 mg omeprazole daily.

Lidocaine

No interaction with a single intravenous dose of lidocaine or its active metabolite, MEGX, was found after one week of pretreatment with LOSEC 40 mg once daily. There were no interactions between omeprazole and lidocaine or MEGX concerning pharmacokinetic variables.

Quinidine

After one week of omeprazole 40 mg once daily, no effect was observed on the kinetics or pharmacodynamics of quinidine.

Ethanol

There was no significant effect on the pharmacokinetics of ethanol after omeprazole 20 mg.

Piroxicam, Diclofenac and Naproxen

There was no significant effect on the steady-state pharmacokinetics of piroxicam, diclofenac, and naproxen following repeated dosing with omeprazole 20 mg in healthy volunteers.

Antacids

No interaction with concomitantly administered antacids has been found.

Food

No interaction with food has been found.

Other Interactions

As demonstrated with other PPIs, prolonged use may impair the absorption of protein-bound Vitamin B₁₂ and may contribute to the development of Vitamin B₁₂ deficiency.

ADVERSE REACTIONS

Omeprazole is well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with the treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole or reported from routine use. In a controlled clinical trial comparing omeprazole to placebo, the prevalence of adverse events with omeprazole 40 mg once daily was similar to the placebo group. In short-term, comparative, double-blind studies with histamine H₂-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole and the H₂-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important.

The following adverse events (at a rate of more than one percent) have been reported in individuals receiving omeprazole therapy in controlled clinical situations: diarrhea (2.8%); headache (2.6%); flatulence (2.3%); abdominal pain (1.7%); constipation(1.3%); and dizziness/vertigo (1.1%).

The following is a list of adverse events reported in clinical trials or reported from routine use. Events are classified within body system categories. The following definitions of frequencies are used: common: $\geq 1/100$; uncommon: $\geq 1/1000$ and $<1/100$; and rare: $<1/1000$.

Central and Peripheral Nervous System: Common: headache. Uncommon: dizziness, paraesthesia, somnolence, insomnia and vertigo. Rare: reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.

Endocrine: Rare: gynaecomastia.

Gastrointestinal: Common: diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence. Rare: dry mouth, stomatitis and gastrointestinal candidiasis.

Hematological: Rare: leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

Hepatic: Uncommon: increased liver enzyme levels. Rare: encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice and hepatic failure.

Musculoskeletal: Rare: arthralgia, muscular weakness and myalgia.

Skin: Uncommon: rash, dermatitis and/or pruritus, and urticaria. Rare: photosensitivity, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis (TEN) and alopecia.

Other Adverse Events: Uncommon: malaise, hypersensitive reactions including urticaria. Rare: hypersensitive reactions including angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock; increased sweating, peripheral edema, blurred vision, taste disturbances and hyponatraemia.

***H. pylori* Eradication Combination Therapy:** The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 493 patients receiving omeprazole, amoxicillin and clarithromycin: diarrhea (28%), taste disturbances (15%), headache (5%), flatulence (4%), nausea (3%), abdominal pain (2%), ALT increased (1%), epigastric pain (1%), pharyngitis (1%) and glossitis (1%).

The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 494 patients receiving omeprazole, metronidazole and clarithromycin: taste disturbances (14%), diarrhea (13%), headache (6%), ALT increased (6%), flatulence (5%), nausea (5%), AST increased (5%), dyspepsia (3%), dry mouth (2%), dizziness/vertigo (2%), epigastric pain (1%), pharyngitis (1%), eructation (1%) and fatigue (1%).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

No information is available on the effects of higher doses in man and specific recommendations for treatment cannot be given. Single oral doses of up to 400 mg of omeprazole have not resulted in any severe symptoms and no specific treatment has been needed. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

The oral LD₅₀ of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign of acute toxicity was vomiting which occurred at doses of approximately 600 mg/kg (see TOXICOLOGY).

When used in combination with antibiotics, the Prescribing Information/Product Monograph for those antibiotics should be consulted.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dose is 20 mg given once daily. Healing usually occurs within two weeks. For patients not healed after this initial course of therapy, an additional two weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg or 40 mg given once daily. Healing is usually achieved within four weeks in such patients.

Maintenance Therapy for Duodenal Ulcer: Over 95% of duodenal ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended LOSEC (omeprazole) dose is 10 mg once daily, increased to 20-40 mg once daily, as necessary.

Gastric Ulcer

Acute Therapy: The recommended adult dose is 20 mg given once daily. Healing usually occurs within four weeks. For patients not healed after this initial course of therapy, an additional four weeks of treatment is recommended.

Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, the recommended dose is 40 mg given once daily. Healing is usually achieved within eight weeks.

Maintenance Therapy for Gastric Ulcer: About 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended LOSEC dose is 20 mg once daily, increased to 40 mg once daily, as necessary.

NSAID-Associated Gastric or Duodenal Ulcers

The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial preventive effects has not yet been settled.

Acute Therapy: In patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily. Symptom resolution is rapid and healing usually occurs within four weeks. For those patients not healed after this initial course of therapy, an additional four weeks of treatment is recommended.

Maintenance Therapy: For the prevention of relapse in patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily, for up to six months.

***Helicobacter pylori*-Associated Peptic Ulcer Disease**

Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days. This dosing regimen can be known as Losec 1-2-3 A[®].

Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days. This dosing regimen can be known as Losec 1-2-3 M[®].

To ensure healing and/or symptom control, further treatment with 20 mg LOSEC once daily for up to three weeks is recommended for patients with active duodenal ulcer, and with 20-40 mg LOSEC once daily for up to 12 weeks for patients with active gastric ulcer.

Patient compliance with treatment regimens for the eradication of *H. pylori* has been demonstrated to have a positive effect on eradication outcome. In clinical trials, patients treated with triple-therapy regimens have shown high compliance rates.

Susceptibility testing (MIC values derived from the Agar dilution method) of *H. pylori* to metronidazole and clarithromycin is available for 486 primary isolates from patients with a history of duodenal ulcer in one European study.

Resistance to metronidazole (MIC >8 mg/L) was detected in 131 strains (27%), while nine strains (2%) were resistant to clarithromycin (MIC >1 mg/L). Secondary resistance to metronidazole developed in strains from four patients treated with omeprazole/metronidazole/clarithromycin. Similarly, in those patients treated with omeprazole/metronidazole/clarithromycin or omeprazole/amoxicillin/clarithromycin combinations, secondary resistance to clarithromycin developed in strains from four patients. For amoxicillin, the MIC values at pre- or post-therapy did not indicate any primary, or the development of secondary, resistance of *H. pylori*.

Reflux Esophagitis

Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within four weeks. For patients not healed after this initial course of therapy, an additional four weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended dose is 40 mg given once daily. Healing is usually achieved within eight weeks.

Maintenance Therapy for Reflux Esophagitis: For the long-term management of patients with healed reflux esophagitis, 10 mg omeprazole once daily has been found to be effective in controlled clinical trials of 12 months' duration, and in continuous maintenance treatment in a limited number of patients for a period of up to six years. In the case of recurrence, the dose can be increased to 20-40 mg omeprazole.

Symptomatic Gastroesophageal Reflux Disease (*i.e.*, Heartburn and Regurgitation)

The recommended adult dose is 20 mg given once daily. Symptom relief should be rapid. If symptom control is not achieved after four weeks, further investigation is recommended. Since some patients respond adequately to 10 mg given once daily, individual dose adjustment should be considered. For the maintenance of symptom relief in patients with gastroesophageal reflux disease (*i.e.*, heartburn and regurgitation), the recommended adult dose is 10 mg given once daily.

Zollinger-Ellison Syndrome

The dose used in the treatment of Zollinger-Ellison Syndrome will vary with the individual patient.

The recommended initial dose is 60 mg, given once daily. More than 90% of the patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20 mg to 120 mg daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered.

Patients with Renal Insufficiency: No dose adjustment is required (see PRECAUTIONS).

Patients with Hepatic Insufficiency: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

Elderly Patients: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

The capsules should be swallowed whole with sufficient water.

PHARMACEUTICAL INFORMATION

Drug Substance	
Proper name	omeprazole
Chemical Name	5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole
Structural Formula	
Molecular Formula	C ₁₇ H ₁₉ N ₃ O ₃ S
Molecular Weight	345.4
Description	Omeprazole is a nonhygroscopic, crystalline substance which melts with decomposition at about 150°C. The substance is slightly soluble in water. The pKa of the benzimidazole is 8.8 and that of the pyridinium ion, 4.0.

Composition

<u>Active:</u>	Omeprazole	mg/capsule
		10
		20

Nonmedical:

10 and 20 mg capsule:

lactose anhydrous
hydroxypropyl cellulose
titanium dioxide
mannitol
iron oxide
microcrystalline cellulose
sodium lauryl sulphate
disodium hydrogen phosphate dihydrate

10 and 20 mg capsule:

hydroxypropyl methylcellulose

methacrylic acid copolymer

polyethylene glycol

magnesium stearate

gelatin

Caloric Content: \approx 3 kJ/capsule

Stability and Storage Recommendations

LOSEC (omeprazole) capsules are moisture sensitive and are therefore provided in a package suitable for direct distribution to the patient.

Patients should be advised to keep the bottle tightly capped and to store it in a dry place. Store at controlled room temperature (15-30°C), protected from moisture.

AVAILABILITY OF DOSAGE FORMS

LOSEC (omeprazole) 10 mg delayed release capsules are two-piece hard gelatin capsules with an opaque pink body and an opaque pink cap. The body is printed '10', and the cap 'A', in
OS

black ink.

LOSEC 20 mg delayed release capsules are two-piece hard gelatin capsules with an opaque pink body and an opaque reddish-brown cap. The body is printed '20', and the cap 'A', in
OM

black ink.

The 10 mg and 20 mg capsules are provided in high-density polyethylene bottles of 30 capsules with a child-resistant screw cap which contains a desiccant. The capsules should be dispensed in the original container.

INFORMATION FOR THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

 LOSEC®

(omeprazole delayed release capsules)

Read this leaflet carefully. It contains general points about LOSEC and should add to more specific advice from your doctor or pharmacist.

WHAT IS LOSEC USED FOR AND HOW DOES IT WORK?

LOSEC is the brand name for a drug called omeprazole.

The most common uses of LOSEC are:

- for stomach ulcers or for duodenal ulcers, including ulcers caused by infection with a bacterium called *Helicobacter pylori*;
- for ulcers caused by your medicine for pain and joint problems (NSAID-associated gastric and duodenal ulcers);
- for reflux esophagitis (tissue damage caused by stomach contents flowing back up the food pipe);
- and for symptoms of reflux disease such as heartburn and regurgitation.

LOSEC may also be used in rare conditions like “Zollinger-Ellison syndrome,” where the stomach produces large amounts of acid. LOSEC works by reducing the amount of acid made in your stomach. This helps in treating acid-related and bacteria-related stomach problems.

Your doctor will have explained why you are being treated with LOSEC and will have told you what dose to take. Follow those directions carefully. They may differ from the information contained in this leaflet.

WHAT IS IN LOSEC?

Each LOSEC capsule contains omeprazole as the active ingredient. In addition, it contains the following non-medicinal ingredients (listed in alphabetical order): disodium hydrogen phosphate dihydrate, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, mannitol, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol and sodium lauryl sulphate.

The 10 and 20 mg capsule shells also contain iron oxide and titanium dioxide as colouring agents.

Check with your doctor if you think you might be allergic to any of the above ingredients.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING LOSEC?

Tell your doctor

- about **all** health problems you have now or have had in the past;
- about severe liver problems you have now or have had in the past;
- about other medicines you take, including ones you can buy without a prescription. Drug effects may be influenced if LOSEC is taken at the same time as some drugs used to prevent fungal infections (itraconazole, ketoconazole, voriconazole), anxiety (diazepam), epilepsy (phenytoin), blood clotting (warfarin or other vitamin K blockers) and in transplant patients (tacrolimus);
- if you are taking medication for HIV. LOSEC may decrease the effectiveness of some drugs used for HIV treatment; atazanavir and nelfinavir should not be used with LOSEC;
- if you are taking clopidogrel, which is used for the prevention of blood clots. LOSEC may interact with this drug, therefore use with clopidogrel is not recommended;
- if you are pregnant, plan to become pregnant or are breastfeeding.

WHEN SHOULD LOSEC NOT BE USED?

If you are allergic to omeprazole or any of the other ingredients in LOSEC (see “What is in LOSEC?”).

HOW DO I TAKE LOSEC PROPERLY?

Take all doses of LOSEC, as recommended by your doctor, even when you feel well. Daily doses are needed to help damaged areas heal. In general, the recommended dose for treating acute disease is 10-40 mg once a day for 2-8 weeks. Your doctor may recommend that you continue taking LOSEC 10-40 mg to control symptoms of reflux disease or to prevent reflux esophagitis from coming back, or LOSEC 20 mg to prevent ulcers from returning while you continue to take your medicine for pain and joint problems.

LOSEC may be used in combination therapy with antibiotic drugs for one week to treat ulcers caused by *Helicobacter pylori*. Your prescription may say Losec[®] 1-2-3 A[®] (which includes clarithromycin and amoxicillin) or Losec[®] 1-2-3 M[®] (which includes clarithromycin and metronidazole). This tells the pharmacist to give you three different drugs (LOSEC and two antibiotics), for you to take two times a day for one week. If your ulcer is bothering you, your doctor may recommend further treatment with LOSEC to make sure that your ulcer is healed.

If you are given LOSEC in combination with antibiotic drugs, it is important that you take all medications at the correct time of day and for the entire treatment period, to ensure they will work properly. Studies have shown that patients who take their medications as prescribed have better ulcer healing rates and greater success getting rid of their *H. pylori* infection.

Take LOSEC until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if LOSEC is stopped too soon. LOSEC needs to be taken for the full duration of treatment to help correct acid problems.

If you miss a dose of LOSEC and remember within 12 hours, take it as soon as possible. Then go back to your regular schedule. However, if more than 12 hours have passed when you remember, do not take the missed capsule. Do not double the dose. Just take your next dose on time.

LOSEC may be taken with food or on an empty stomach.

ARE THERE ANY SIDE EFFECTS?

Like any medication, LOSEC may cause side effects in some people. Side effects that do occur are usually mild and go away a short time after starting LOSEC.

Talk with your doctor if you suffer from any of these effects or if you get any other unusual or unexpected symptoms. These side effects may not be caused by LOSEC in your case, but only a doctor can assess this.

Common side effects that may occur (frequency of greater than or equal to 1 in 100 patients):

- Headache, diarrhoea, constipation, abdominal pain, nausea/ vomiting, and excess gas in stomach (flatulence).

Uncommon side effects that may occur (frequency of greater than or equal to 1 in 1000 patients, but less than 1 in 100 patients):

- Dizziness, sensation of movement of one's self or of one's surroundings (vertigo), difficulty sleeping, feeling sleepy, sensation of burning/ prickling/ numbness, skin reactions (such as skin rash, dermatitis, itchy skin and/or hives) and feeling ill.

Rare side effects that may occur (frequency of less than 1 in 1000 patients):

- Dry mouth, inflammation in the mouth, gastrointestinal fungal infection, kidney and liver problems (i.e., inflammation of the kidney, inflammation of the liver with or without jaundice, impaired liver function), blood disorders (reduced number of cells in the blood, low blood sodium), sore joints and muscles, muscular weakness, development of breasts in males, sensitivity to sunlight, severe skin reactions, hair loss, hypersensitive (allergic) reactions (such as swelling of tissues, fever, discomfort/ tightness in chest and anaphylactic shock), increased sweating, blurred vision, and taste disorders. If you already have severe liver disease, you may experience disorientation/ aggression/ confusion/ decreased consciousness. If you are very ill, you may feel confused, nervous, depressed or hallucinate.

Other unwanted effects, which cannot be predicted, may occur in rare cases. If you experience any bothersome or unusual effects while using LOSEC, check with your doctor or pharmacist right away.

WHAT SHOULD I DO IN CASE OF OVERDOSE?

Call your doctor, pharmacist or regional poison control centre right away in case of an overdose. However, no severe symptoms have been seen in patients who have taken doses up to 400 mg.

WHERE SHOULD I KEEP LOSEC?

Keep all capsules in their container until it is time for a dose. If you do not, moisture from the air may damage the capsules.

Remember to keep LOSEC well out of reach of children. Keep the package at room temperature (15-30°C). Do not keep LOSEC in the bathroom medicine cabinet or other warm, moist places.

Do not use LOSEC after the expiry date marked on the pack.

Important Note:

This leaflet alerts you to some of the times you should call your doctor. If you experience symptoms that may indicate a more serious stomach or intestinal problem, you should contact your doctor immediately. Such symptoms may include any of the following: difficulty swallowing, unintentional weight loss, vomiting blood or food, or black (blood-stained) stools. Other situations, which cannot be predicted, may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using LOSEC.

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing. Please refer to the Consumer Information Leaflet located at www.astrazeneca.ca, to see if more up-to-date information has been posted.

For additional information on acid-related diseases, please call 1 800 668-6000.

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PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Omeprazole differs from existing inhibitors of gastric acid secretion such as histamine H₂-receptor antagonists or anticholinergic agents in its ability to directly inhibit the gastric H⁺, K⁺-ATPase. This enzyme has been identified as the proton pump of the parietal cell.

Omeprazole had a long duration of action in all species studied. Repeated daily doses resulted in a progressive increase in the antisecretory effect during the first 3-5 days of administration. In dogs, a dose of 0.5 µmol/kg (given as enteric-coated granules) inhibited histamine stimulated gastric acid secretion by about 20% when measured 24 hours after the first dose, and by 60-65% when measured 24 hours after dosing at steady state. Once steady-state conditions were reached (after 3-5 days), acid inhibition remained unchanged, as established in dogs treated for periods up to one year.

Acid secretion recovers after discontinuation of long-term treatment at the same rate as after a single dose of omeprazole, in parallel with the recovery of H⁺, K⁺-ATPase activity in the oxyntic mucosa. Whether this recovery reflects *de novo* synthesis of the H⁺, K⁺-ATPase molecules or the dissociation of the inhibitor from the enzyme has not yet been established.

Due to the potency and long duration of action of omeprazole, repeated administrations of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells. In rats, administration of omeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 1000-3000 pg/mL as compared to 150-200 pg/mL in controls. In dogs, high doses of omeprazole (28 mg/kg/day) produced marked hypergastrinemia (1000-2000 pg/mL after food intake), as compared to 100-300 pg/mL in controls. However, no hyperplasia of G-cells was evident in this species.

Secondary Pharmacological Effects

Mean arterial blood pressure and heart rate in the anesthetized dog were not affected by omeprazole under various challenges. Circulatory and respiratory functions in the dog were not affected by omeprazole, either at rest or during exercise. Omeprazole had no anticholinergic and no antihistamine (H₂-receptor) activity. In the rat, no effect on basal locomotor activity nor on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Other Interactions

Omeprazole interacts with cytochrome P-450 in rat liver. Omeprazole prolonged hexobarbital sleeping time by 12%.

Pharmacokinetics

Absorption and Distribution: Omeprazole is degraded rapidly in acidic gastric juice (rat and dog studies). Absorption is rapid. Peak plasma levels were found within 20 minutes and one

hour after intra-duodenal and oral administration, respectively, in the dog. The drug has a low oral bioavailability, 5% in unstarved rats and 15-20% in starved male and female rats, if the drug is not protected by an enteric coating. The intra-duodenal bioavailability is approximately 70% and the oral bioavailability is approximately 15% in the dog. After absorption, omeprazole is rapidly distributed to extravascular sites and about 95% is bound to plasma proteins. The distribution of ¹⁴C-labelled omeprazole in the mouse was investigated by autoradiography. Radioactivity was initially found in the blood and most organs. Sixteen hours after administration, the drug was confined predominantly to the stomach wall. At 48 hours, the radioactivity was eliminated.

Penetration of omeprazole and/or its metabolites across the blood-brain and placental barriers was low.

Metabolism and Excretion: Omeprazole was extensively metabolized in all species studied. In rats and dogs approximately 20-30% of the dose was excreted as urinary metabolites and the remainder by biliary excretion as metabolites in the feces. Elimination was virtually complete within 72 hours. Identifiable metabolites constituted about 50% (rat) and 70% (dog) of the total metabolite excretion in 24 hours, and about 12% of the given dose in both species.

A study in lactating rats showed that omeprazole is excreted in breast milk. The concentration in the milk at 3-5 hours postdose was 100-200 times lower than the plasma concentration. It is not known if omeprazole is excreted in human milk.

Human Pharmacology

Pharmacodynamics

In both normal volunteers and hypersecretors, omeprazole inhibited basal nocturnal and daytime acid secretion as well as meal-, histamine-, and pentagastrin-stimulated secretion.

Table 3 Percentage inhibition of mean acid output after single oral doses of omeprazole.

STIMULUS	TYPE OF SUBJECT	OMEPRAZOLE DOSE		TIME AFTER DOSE (h)
		20 mg	80 mg	
Basal	HSu*	33%		1-4
Basal-Nocturnal	DU(rem)**	49%		15-24
Sham Feeding	HSu	23%		1.5-3.5
Betazol	HSu	38%		1-4
Pentagastrin	HSu	36%		1-4
Basal	ZES***		97%	2-3

* healthy subject

** duodenal ulcer in remission

*** Zollinger-Ellison Syndrome

Repeated oral dosing with 20 mg of omeprazole once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first four days of treatment. Gastric emptying was unaffected by omeprazole

In duodenal ulcer patients, a mean decrease in 24-hour intragastric acidity of about 80% was then maintained. The mean decrease in peak acid output after pentagastrin stimulation was about 70% 24 hours after repeated dosing with omeprazole 20 mg. Omeprazole caused a transient decrease in stimulated pepsin output which resolved within four hours of dosing. Omeprazole had no effect on intrinsic factor secretion.

Decreased gastric acidity due to the use of acid suppressing medications, including any proton pump inhibitors, is associated with increased gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to a slightly increased risk of *Salmonella* and *Campylobacter* gastrointestinal infections.

Other Pharmacodynamic Effects

The effect of omeprazole on various organ systems has been investigated. **No clinically significant effects** attributable to the drug could be found for the following parameters: *Endocrine*: plasma levels of insulin, C-peptide, glucagon, PTH, thyroid hormones or sex hormones, basal levels of cortisol; *Cardiovascular*: blood pressure, heart rate, electrocardiogram; *Renal*: renal handling of acid and electrolytes; *Hepatic*: liver enzymes. However, in some patients receiving LOSEC, elevated concentrations of alkaline phosphatase, S-AST and S-ALT have been reported (see ADVERSE REACTIONS).

No clinically significant CNS effects have been recorded.

No clinically significant effects on other organ systems have been noted.

Omeprazole has no effect on acetylcholine or H₂-receptors.

Pharmacokinetics

LOSEC is rapidly absorbed. After an initial oral dose of omeprazole, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. After oral administration, peak plasma levels occur within about four hours. The terminal plasma half-life is approximately 40 minutes; the total plasma clearance is 0.6 L/min. Although the antisecretory effect of omeprazole is directly proportional to the AUC, it is not dependent on the plasma concentration at any given time.

The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC (geometric ratio and 90% confidence interval: 1.18, 1.06-1.30), C_{max} (1.41, 1.24-1.60) and T. LOSEC 20 mg tablets demonstrate, after repeated dosing, increased plasma omeprazole AUC (18%) and maximum concentration (41%) in comparison to omeprazole 20 mg given as capsules.

LOSEC is 95% bound to plasma proteins.

Ninety-five to 100% of duodenal ulcer and 80% of gastric ulcer patients are *H. pylori*-positive and should be treated with eradication therapy. Eradication of *H. pylori* is associated with long-term remission of peptic ulcer disease. Long-term treatment of these patients with antisecretory agents is generally not recommended. Long-term treatment with omeprazole is effective in the prevention of relapse of duodenal or gastric ulcer, as demonstrated in clinical studies in patients with unknown *H. pylori* status, and may be used for the minority of patients who are *H. pylori*-negative.

The bioavailability of amoxicillin was studied during concomitant administration with omeprazole in fasting healthy adult subjects. When a single dose of amoxicillin, 750 mg, was administered to subjects who had received repeated doses of omeprazole 40 mg twice daily for three weeks, no significant change in the bioavailability (AUC, C_{max}) of amoxicillin was observed.

Clarithromycin 500 mg three times daily and omeprazole 40 mg capsules once daily were studied following concomitant administration in fasting healthy adult subjects. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $t_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max} , C_{min} and AUC_{0-8} of clarithromycin were increased by 10%, 27% and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

The omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine. In contrast to the capsule, the tablet (as a single unit formulation) will enter the intestine and dissolve as one unit. Consequently, the absorption and first pass metabolism of the tablet take place during a very limited period. This may be one of the reasons for the difference observed in the pharmacokinetic variables of the two formulations.

Omeprazole undergoes first-pass metabolism, and is completely metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The major part of its metabolism is dependent upon the polymorphically expressed, specific isoform, CYP 2C19 (S-mephenytoin hydroxylase). Following i.v. and oral administration, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. Less than 0.1% of the dose administered is excreted in urine as unchanged drug.

Six urinary metabolites have been detected. The two main metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. Three metabolites have been identified in plasma, the sulphide and sulphone derivatives and hydroxyomeprazole. It is unlikely that these metabolites contribute to inhibition of acid secretion.

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour). The mean urinary

excretion of metabolites was 68% of the dose. These changes are consistent with reduction in presystemic and systemic elimination, typical in the elderly. The daily dose should, as a rule, not exceed 20 mg in this patient group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of omeprazole in patients with impaired renal function was virtually the same as in healthy subjects. However, patients with impaired liver function showed increased bioavailability (75%), reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours). Twenty mg given once daily to these patients for four weeks was well tolerated. Dosage for patients with liver cirrhosis and other liver dysfunction should, as a rule, not exceed 20 mg daily (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

TOXICOLOGY

Acute Toxicity

Table 4 Acute toxicity studies of omeprazole

Species	SEX	ROUTE	LD50 (mg/kg)
Mouse	M	p.o. ^{1*}	>4000
	F	p.o. ^{1*}	>4000
Mouse	M	p.o. ¹	1520
	F	p.o. ¹	1380
Mouse	M	i.v.	83
	F	i.v.	>100
Rat	M	p.o. ^{1*}	>4000
	F	p.o. ^{1*}	>4000
Rat	M	p.o. ¹	>5010
	F	p.o. ¹	3320
Rat	M	i.v.	>40
	F	i.v.	>40

¹ suspension of Methocel[®], not buffered

* non-micronized test compound

The highest oral dose (4000 mg/kg) of non-micronized omeprazole did not cause death in any of the species tested. With micronized omeprazole, suspended in Methocel[®], the acute oral LD₅₀ was approximately 1500 mg/kg in mice; in male rats, higher than the maximum dose (5000 mg/kg) and in female rats, approximately 3000 mg/kg. As much as 80% of the compound may not have been absorbed due to acid degradation of these single doses in the stomach. Death occurred within two days of ingestion and was preceded by reduced motor

activity, reduced respiration frequency but increased respiration depth, reduced body temperature, and twitching, tremor or convulsions. The highest oral dose given to dogs (660 mg/kg) caused vomiting within 40-100 minutes of ingestion. The acute intravenous LD₅₀ was 83 mg/kg in male mice and in female mice >100 mg/kg. The corresponding figure in rats was >40 mg/kg. Death occurred within a few minutes of injection, preceded by cyanosis and convulsions.

Long-Term General Toxicity

The general, long-term toxicity of omeprazole was studied in mice, rats, and dogs after oral and intravenous administration. Mice received oral doses of 14-140 mg/kg for up to 18 months, rats 14-400 mg/kg for up to 24 months and dogs 1-140 mg/kg for up to 12 months. Intravenous omeprazole was given to rats in doses of 2-16 mg/kg for up to one month and dogs 1-9 mg/kg for up to one month.

In the dog, a slight to moderate atrophy of the chief cells and rugal hypertrophy were observed. These changes were reversible after treatment cessation.

Following chronic intravenous administration of omeprazole to rats (~1.7-15.5 mg/kg/day) for one month and to dogs (~0.7-8.6 mg/kg/day) for one month, no treatment related changes were observed.

In the rat, decreased plasma concentrations of triiodothyronine were observed in the two highest groups; TSH increased in the high-dose males. Lower doses had no significant effect. General hypertrophy of the oxyntic mucosa was found; the size of some chief cells was decreased and some granularity was observed. Both the hypertrophy and chief cell changes were reversible.

Reproduction Studies

In studies with male and female rats given oral doses of up to 138 mg/kg/day (approximately 500 times the recommended human dose), fertility and reproductive performance were not affected.

In rabbits, increased embryo-lethality and fetal resorption were observed at maternotoxic doses of 69 and 138 mg/kg/day (250 and 500 times the human dose). No maternal or fetal toxicity was observed in pregnant rats treated at doses ranging from 13.8 to 138 mg/kg/day (50 to 500 times the human dose). In rats, a slight decrease in litter size at birth and slightly impaired postnatal viability and growth were observed in offspring resulting from parents treated with high doses of 138 mg/kg/day (500 times the human dose) of omeprazole. Similar effects were not seen at lower doses.

Mutagenicity

Omeprazole was tested *in vivo* (mouse micronucleus test, chromosome aberration in mice) and *in vitro* (Ames test, mouse lymphoma forward mutation assay) and showed no evidence of a mutagenic effect.

Carcinogenicity

An 18-month oral study was conducted in mice at doses of 14, 44, and 140 mg/kg/day. No evidence of carcinogenic potential was seen. A 24-month oral study was conducted in rats at doses of 14, 44, and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumour-like proliferations in the stomach. Histology showed a continuum from diffuse ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumour-like proliferations, some extending into the submucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in female rats. No metastases were identified in any of the animals. Carcinoids have not been observed after long-term administration of omeprazole to mice and dogs.

Gastric ECL-Cell Carcinoids

Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. Gastrin produced by the G-cells in the antrum plays an important role in the feedback control of gastric acid secretion.

In one series of experiments, the antrum of rats was surgically excluded from the rest of the stomach. The removal of acid from the antrum in this way led to pronounced hypergastrinemia and, secondary to this, gastric ECL-cell proliferation. Antrectomy, which removes the source of gastrin, led to a decrease in gastric ECL-cell density. These experiments indicated that gastrin has a direct trophic effect on gastric ECL-cells. In another series of experiments, high doses of omeprazole and a histamine H₂-receptor blocker caused hypergastrinemia and increased ECL-cell density. In antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that (i) inhibition of gastric acid secretion by large doses of omeprazole, or a histamine H₂-receptor blocker, evokes a natural feedback response leading to hypergastrinemia, (ii) long-standing hypergastrinemia leads to gastric ECL-cell proliferation, and (iii) there is no direct trophic effect of omeprazole on gastric ECL-cells.

An additional long-term (24 months) toxicity study in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumours and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found and the ECL-cell hyperplasia recovered to normal during the next 12 months of no treatment.

No carcinoids have been found in mice, and in dogs following administration of 28 mg/kg/day for seven years.

Investigation in man has demonstrated an initial moderate increase in gastrin levels during treatment with omeprazole, but no further increase occurred during long-term (up to three years) treatment. No significant changes have been found in the endocrine cells of the oxyntic gastric mucosa during short- or long-term treatment with omeprazole in man, to date. Chronic treatment of patients with Zollinger-Ellison Syndrome with mean daily doses of omeprazole

of 60 mg/day for up to five years has not influenced the pretreatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

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