

## PRODUCT MONOGRAPH

**LOSEC MUPS™**

(omeprazole magnesium delayed release tablets)

10 mg and 20 mg omeprazole

H<sup>+</sup>,K<sup>+</sup>-ATPase Inhibitor

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LOSEC MUPS™, LOSEC 1-2-3 A® and LOSEC 1-2-3 M® are trade-marks of the AstraZeneca group of companies.

## PRODUCT MONOGRAPH

### NAME OF DRUG

 LOSEC MUPS™

omeprazole magnesium delayed release tablets

10 mg and 20 mg omeprazole

### THERAPEUTIC CLASSIFICATION

H<sup>+</sup>,K<sup>+</sup>-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

Omeprazole inhibits the gastric enzyme H<sup>+</sup>,K<sup>+</sup>-ATPase (the proton pump) which catalyses the exchange of H<sup>+</sup> and K<sup>+</sup>. Omeprazole 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.

Treatment with omeprazole alone has been shown to suppress, but not eradicate *Helicobacter pylori* (*H. pylori*), a bacterium that is strongly associated with acid peptic disease. Ninety to 100% of patients with duodenal ulcers are infected with this pathogen.

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 anti-secretory therapy.

When omeprazole was administered in combination with amoxicillin and clarithromycin to healthy volunteers, there was no clinically significant change in the bioavailability (AUC, C<sub>max</sub>) of amoxicillin (ratio of AUC values and 95% CI: 1.10; 1.00-1.22). An increase in the bioavailability (AUC) of omeprazole was noted (2.10; 1.85-2.38) and slight increases were seen in the plasma levels of 14-hydroxycarithromycin (1.34; 1.15-1.57). The plasma levels of clarithromycin were similar when it was administered alone or in combination with omeprazole and amoxicillin (1.14; 0.95-1.36).

There is no statistically significant change in the bioavailability (AUC, C<sub>max</sub>) of metronidazole during concomitant treatment with omeprazole, in healthy volunteers.

The antisecretory effect of omeprazole is correlated to the area under the plasma concentration versus time curve (AUC), but it is independent of the peak plasma concentration ( $C_{max}$ ).

LOSEC MUPS tablets are absorbed rapidly. Food has no effect upon the bioavailability of the tablet (AUC), but results in a 30% decrease in peak plasma concentration. However, given the lack of relationship between the peak concentration and the antisecretory effect of omeprazole, LOSEC MUPS tablets may be taken with or without food.

After oral administration, omeprazole undergoes first-pass metabolism by the cytochrome P-450 2C19 system, mainly in the liver. The absolute bioavailability is about 60% after repeated oral dosing (20 mg capsules). Following i.v. administration and oral administration of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. Omeprazole is 95% bound to plasma proteins.

The pharmacokinetics of omeprazole are complex with blood levels increasing more than proportionally with increasing dose (20 to 40 mg), and after repeated administration. These increases are probably the result of saturable first-pass metabolism of omeprazole.

CYP 450 2C19 is a polymorphic enzyme. This heterogeneity is more pronounced in the Asian population where the proportion of slow metabolizers is higher than in Caucasians. 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. The half-life of omeprazole in slow metabolizers is about 2.5 hours as compared to approximately 1 hour for rapid metabolizers. It is recommended that Asian populations be closely followed-up, particularly when doses are higher than 20 mg and/or there is concomitant hepatic disease.

LOSEC MUPS tablets and LOSEC capsules of corresponding strength have comparable bioavailability, in terms of plasma AUC and  $C_{max}$  in healthy volunteers. The 20 mg MUPS tablets and the 20 mg capsules have an equivalent pharmacodynamic effect as assessed by the effect on the proportion of time during a 24-hour period in which intragastric pH is  $\geq 4$  in patients with symptomatic gastroesophageal reflux disease.

## INDICATIONS AND CLINICAL USE

LOSEC MUPS (omeprazole magnesium) tablets are 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
- dyspepsia\*: a complex of symptoms which may be caused by any of the organic diseases listed above, or upon investigation no identifiable organic cause is found (i.e., functional dyspepsia);

- 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. Eradication of *H. pylori* has been shown to reduce the risk of peptic ulcer recurrence. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (i.e., asymptomatic) remains to be determined.

In dyspeptic patients with an *H. pylori* infection, the concurrent gastritis can be healed with appropriate eradication therapy.

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).

- \* A working definition of dyspepsia would include the presence of epigastric pain/discomfort, with or without heartburn and regurgitation which may be accompanied by nausea, vomiting, bloating, belching, flatulence, early satiety or post-prandial fullness. Symptoms may occur either during the day or throughout the night.

**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 of 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 MUPS (omeprazole magnesium) tablets is instituted, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

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

### Use in Pregnancy

The safety of omeprazole in pregnancy has not been established. LOSEC MUPS tablets 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 MUPS tablets should not be given to nursing mothers unless its use is considered essential.

### Use in Children

The safety and effectiveness of LOSEC MUPS tablets in children have 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) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). 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) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg omeprazole capsules given once daily to these patients for 4 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 (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules) (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 7 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 H<sub>2</sub>-receptor blockers and also in partially fundectomized rats.

Short-term treatment and long-term treatment with omeprazole capsules in a limited number of patients for up to 6 years have 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 capsules in humans: aminopyrine, antipyrine, 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.

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

As LOSEC MUPS 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 capsules 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 capsules versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on 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's pre-treatment with omeprazole 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 antacids administered concomitantly with omeprazole (given as capsules) has been found.

### Other Interactions

As demonstrated with other PPIs, prolonged use may impair the absorption of protein-bound Vitamin B<sub>12</sub> and may contribute to the development of Vitamin B<sub>12</sub> deficiency.

## **ADVERSE REACTIONS**

Omeprazole is well tolerated. Most adverse reactions have been mild and transient, and have shown no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole (data taken from controlled clinical studies with omeprazole capsules) 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 that with placebo. In short-term comparative double-blind studies with histamine H<sub>2</sub>-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole capsules and the H<sub>2</sub>-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important.

In two short term studies (20 mg tablet once daily for a maximum duration of 7 days) in a limited number of patients with symptomatic gastroesophageal reflux disease, the adverse event profile seen with the LOSEC MUPS 20 mg tablet is similar to that seen with the LOSEC 20 mg capsule.

The following adverse events (at a rate of more than 1%) have been reported in individuals receiving omeprazole capsules 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, paresthesia, somnolence, insomnia and vertigo. Rare: reversible mental confusion, agitation, aggression, depression and hallucination occurring 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-Johnson syndrome, toxic epidermal necrolysis (TEN) and alopecia.

**Other Adverse Events:** Uncommon: malaise, hypersensitive reactions including urticaria. Rare: hypersensitive reactions including angioedema, fever, bronchospasm and 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 capsules 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 LD<sub>50</sub> 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 an antibiotic, the Prescribing Information/Product Monograph for that antibiotic should be consulted.

## DOSAGE AND ADMINISTRATION

LOSEC MUPS (omeprazole magnesium) 20 mg tablets and LOSEC 20 mg capsules have an equivalent effect on 24-hour intragastric pH (proportion of time with intragastric pH  $\geq$  4). These data support the conclusion that LOSEC MUPS tablet and the LOSEC capsule can be used with equal efficacy in the treatment of conditions where a reduction of gastric acid secretion is required.

### Duodenal Ulcer

Acute Therapy: The recommended adult oral dose is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg and 40 mg given once daily. Healing is usually achieved within 4 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 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 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with benign gastric ulcer refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 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 MUPS 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 4 weeks. For those patients not healed after this initial course of therapy, an additional 4 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 6 months.

### **Dyspepsia**

Prior to treating patients presenting with dyspeptic symptoms, it should be determined that these symptoms are originating from the upper gastrointestinal tract. Patients presenting alarm symptoms (see WARNINGS), and older patients who are at a greater risk of having a serious organic disease, should be investigated prior to the initiation of therapy. If the dyspeptic symptoms are known to be related to a diagnosis of organic disease, the appropriate treatment regimen listed in the sections above should be employed.

If the dyspeptic symptoms are not known to be related to an organic disease, the recommended daily dose of LOSEC MUPS is 20 mg once daily for 4 weeks. If after 2 weeks' 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 (see WARNINGS). If there are indications of a clinical response following the initial 2 weeks of treatment, LOSEC MUPS may be continued for an additional 2 weeks. Patients

may respond adequately to 10 mg once daily therefore, individual dose adjustment may be considered.

Epigastric pain/discomfort (with or without heartburn and regurgitation) as predominant symptoms, are likely to respond to acid suppression therapy. In all cases, patients who do not respond to 4 weeks' treatment, or whose symptoms recur shortly after discontinuation of treatment, with LOSEC MUPS should be investigated for underlying organic diseases.

### ***Helicobacter pylori* Associated Peptic Ulcer Disease**

Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC MUPS 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<sup>®</sup>.

Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC MUPS 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<sup>®</sup>.

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 twelve 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 9 strains (2%) were resistant to clarithromycin (MIC >1 mg/L). Secondary resistance to metronidazole developed in strains from 4 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 4 patients. For amoxicillin, the MIC values at pre-therapy or post-therapy did not indicate any primary, or the development of secondary, resistance to *H. pylori*.

### **Reflux Esophagitis**

Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Reflux Esophagitis: For the long-term management of patients with healed reflux esophagitis, 10 mg omeprazole (given as capsules) 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 6 years. Therefore, the recommended adult dose of LOSEC MUPS tablets for maintenance treatment of patients with healed reflux esophagitis is 10 mg given once daily. In the case of recurrence, the dose can be increased to 20-40 mg once daily.

### **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 4 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 patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20-120 mg omeprazole capsules 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 omeprazole capsules three times daily 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 MUPS tablets should be swallowed whole with sufficient water.

## PHARMACEUTICAL INFORMATION

Drug Substance	
Proper name	omeprazole magnesium
Chemical Name	Di (5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole) magnesium
Structural Formula	
Molecular Formula	C <sub>34</sub> H <sub>36</sub> N <sub>6</sub> O <sub>6</sub> S <sub>2</sub> Mg
Molecular Weight	713.1 (anhydrous basis)
Description	Omeprazole magnesium is a white to off-white crystalline powder, containing between 2 and 4 waters of hydration. The solubility in water is 0.25 g/L, and the solubility in methanol is 10 g/L. The pKa of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion, 4.0.

### Composition

#### Active:

	mg/tablet
omeprazole magnesium anhydrous	10.3 (corresponds to 10 mg omeprazole/tablet)
	20.6 (corresponds to 20 mg omeprazole/tablet)


#### Nonmedicinal:


microcrystalline cellulose  
 glyceryl monostearate  
 hydroxypropylcellulose  
 hydroxypropyl methylcellulose  
 magnesium stearate  
 sodium stearyl fumarate  
 methacrylic acid copolymer  
 sugar spheres  
 polyethylene glycol  
 polysorbate  
 polyvinylpyrrolidone crosslinked  
 talc  
 titanium dioxide  
 triethyl citrate  
 iron oxides (reddish brown and yellow)  
 paraffin

### **Stability and Storage Recommendations**

LOSEC MUPS (omeprazole magnesium) tablets are moisture sensitive and are therefore provided in a high density polyethylene bottle or a blister compliance package suitable for direct distribution to the patient. Store in tightly-closed original containers at controlled room temperature (15-30°C), protected from moisture.

### **AVAILABILITY OF DOSAGE FORMS**

LOSEC MUPS (omeprazole magnesium) 10 mg delayed release tablets are light pink, oblong, biconvex and film-coated engraved with  on one side and 10 mg on the other side.

LOSEC MUPS 20 mg delayed release tablets are pink, oblong, biconvex and film-coated engraved with  on one side and 20 mg on the other side.

The MUPS tablets are provided in bottles of 50 tablets and must be dispensed in the original container.

## INFORMATION FOR THE CONSUMER

### IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

 LOSEC MUPS™

(omeprazole magnesium delayed release tablets)

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

#### **WHAT IS LOSEC MUPS USED FOR AND HOW DOES IT WORK?**

LOSEC MUPS is the brand name for a drug called omeprazole.

The most common uses of LOSEC MUPS 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 dyspepsia, a group of symptoms which may include stomach pain/discomfort, heartburn and regurgitation. Dyspepsia can be caused by the other conditions in this list.

LOSEC MUPS may also be used in rare conditions like “Zollinger-Ellison syndrome,” where the stomach produces large amounts of acid. LOSEC MUPS 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 MUPS?**

Each LOSEC MUPS tablet contains omeprazole as the active ingredient. In addition, it contains the following non-medicinal ingredients (listed in alphabetical order): glyceryl monostearate, hydroxypropylcellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol, polysorbate, polyvinylpyrrolidone crosslinked, sodium stearyl fumarate, sugar spheres, talc, titanium dioxide and triethyl citrate.

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 MUPS?

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 pregnant, plan to become pregnant or are breastfeeding.

## WHEN SHOULD LOSEC MUPS NOT BE USED?

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

## HOW DO I TAKE LOSEC MUPS PROPERLY?

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

LOSEC MUPS 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<sup>®</sup> (which includes clarithromycin and amoxicillin) or Losec 1-2-3 M<sup>®</sup> (which includes clarithromycin and metronidazole). This tells the pharmacist to give you three different drugs (LOSEC MUPS 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 MUPS to make sure that your ulcer is healed.

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

If you miss a dose of LOSEC MUPS 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 tablet. Do not double the dose. Just take your next dose on time.

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

### **ARE THERE ANY SIDE EFFECTS?**

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

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 MUPS 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 MUPS, 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 MUPS?**

Keep all LOSEC MUPS tablets in the original container until it is time for a dose. If you do not, moisture from the air may damage the LOSEC MUPS tablets.

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

Do not use LOSEC MUPS after the expiry date marked on the container.

### **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 MUPS.

**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](http://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 H<sub>2</sub>-receptor antagonists and anticholinergic agents in its ability to directly inhibit the gastric H<sup>+</sup>, K<sup>+</sup>-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 of 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<sup>+</sup>, K<sup>+</sup>-ATPase activity in the oxyntic mucosa. Whether this recovery reflects *de novo* synthesis of the H<sup>+</sup>, K<sup>+</sup>-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 (H<sub>2</sub>-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 the 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 1 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 <sup>14</sup>C-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 post dose 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 (omeprazole capsule data).

**Table 3**                    **Percentage Inhibition Of Mean Acid Output After Single Oral Doses of Omeprazole.**

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

STIMULUS	TYPE OF SUBJECT	OMEPRAZOLE DOSE (mg)		TIME AFTER DOSE (h)
		20	80	
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 dosing with omeprazole capsule 20 mg once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first 4 days of treatment.

Information from two clinical trials in patients with symptomatic gastroesophageal reflux disease indicates that LOSEC MUPS (omeprazole magnesium) 20 mg tablets demonstrate a similar effect on 24-hour intragastric pH as LOSEC 20 mg capsules after repeated dosing.

**Table 4 Ratios Of The Proportion Of Time During a 24-hour Period With pH ≥ 4 After Repeated Dose Administration Of Omeprazole In Patients With Symptoms Of GERD.**

	Ratio of Proportion of Time with Intragastric pH ≥ 4 (over 24 h) for LOSEC MUPS tablet vs. capsule
<i>Study 1</i>	
20 mg, 6 days	0.99 (95% CI: 0.89 to 1.11)
<i>Study 2</i>	
20 mg, 7 days	1.02 (90% CI: 0.94 to 1.06)

It has also been demonstrated that the LOSEC delayed release (omeprazole magnesium) tablet has a similar effect on 24-hour intragastric pH as LOSEC capsule in patients with DU in remission. Therefore, the clinical efficacy of LOSEC MUPS (omeprazole magnesium) tablet and LOSEC delayed release (omeprazole magnesium) tablet are expected to be similar.

**Table 5 Proportion Of Time During a 24-hour Period With Intragastric pH ≥ 3 In Patients With DU In Remission.**

	Ratio (90% CI) of Proportion of Time with Intragastric pH ≥ 3 (over 24 h) for LOSEC capsule vs. LOSEC tablet
<i>Study 3</i>	
20 mg, 7 days	1.07 (0.99 to 1.16)

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 (data taken from clinical studies using omeprazole capsules). **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 omeprazole, 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 H<sub>2</sub>-receptors.

#### Pharmacokinetics

LOSEC MUPS tablets are absorbed rapidly. Peak plasma levels occur on average within 2 hours. LOSEC MUPS tablets have been compared to the previously available LOSEC capsules of corresponding strength with respect to, in terms of plasma AUC and C<sub>max</sub>, in healthy volunteers.

**Table 6 Pharmacokinetic Measurements Following Administration Of LOSEC MUPS Tablets Or LOSEC Capsules, In Healthy Male Volunteers.**

Dosage	Day	Ratio of AUC values (90% CI)	Ratio of C <sub>max</sub> values	t <sub>max</sub>
20 mg	1	1.02 (0.94-1.11)	1.05	MUPS tablet: 1.84 (0.8) capsule: 1.46 (0.6)
20 mg	6	1.06 (0.95-1.17)	1.03	MUPS tablet: 1.83 (0.8) capsule: 1.57 (0.6)
10 mg	1	1.01 (0.92-1.11)	1.00	MUPS tablet: 1.86 (1.1) capsule: 1.74 (0.6)

The antisecretory effect of omeprazole is correlated to the area under the plasma concentration versus time curve (AUC), but it is independent of the peak plasma concentration (C<sub>max</sub>).

Omeprazole undergoes first-pass metabolism, and is completely metabolized by the CYP-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. administration and oral administration (capsules) of omeprazole, 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) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). 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 (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). However, 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) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg given once daily to these patients for 4 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).

Information on the bioavailability of LOSEC MUPS 20 mg tablet in elderly patients, in patients with hepatic insufficiency, and in patients with renal insufficiency is not currently available.

#### *Helicobacter pylori* eradication using Omeprazole Triple Therapy

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 anti-secretory 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 3 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.

## TOXICOLOGY

### Acute Toxicity

**Table 7 Acute Toxicity Studies Of Omeprazole.**

SPECIES	SEX	ROUTE	LD <sub>50</sub> (mg/kg)
Mouse	M	p.o. <sup>1*</sup>	> 4000
	F	p.o. <sup>1*</sup>	> 4000
Mouse	M	p.o. <sup>1</sup>	1520
	F	p.o. <sup>1</sup>	1380
Mouse	M	i.v.	83
	F	i.v.	>100
Rat	M	p.o. <sup>1*</sup>	> 4000
	F	p.o. <sup>1*</sup>	>4000
Rat	M	p.o. <sup>1</sup>	> 5010
	F	p.o. <sup>1</sup>	3320
Rat	M	i.v.	> 40
	F	i.v.	>40

<sup>1</sup> suspension in Methocel<sup>®</sup>, 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<sup>®</sup>, the acute oral LD<sub>50</sub> 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 2 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 LD<sub>50</sub> 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 to 10 dogs in doses of 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 sub-mucosa. 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 H<sub>2</sub>-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 H<sub>2</sub>-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 7 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 3 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 5 years has not influenced the pre-treatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

## **BIBLIOGRAPHY**

1. AB Astra.  
Omeprazole Monograph.  
Oxford Clinical Communications, 1988.
2. Alumets J, El Munshid HA, et al.  
Effect of antrum exclusion on endocrine cells of rat stomach.  
J Physiol 1979;286:145-155.
3. Andersson T.  
Pharmacokinetics, metabolism and interactions of acid pump inhibitors.  
Clin Pharmacokinet 1996;31:9-28.
4. Bardhan KD, Bianchi Porro G, Bose K, et al.  
A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers.  
J Clin Gastroenterol 1986;8(4):408-413.
5. Brunner G, Creutzfeldt W.  
Omeprazole in the long-term management of patients with acid-related diseases resistant to ranitidine.  
Scand J Gastroenterol 1989;24(Suppl 166):101-105.
6. Cederberg C, Ekenved G, et al.  
Acid inhibitory characteristics of omeprazole in man.  
Scand J Gastroenterol 1985;20(108):105-112.
7. Clissold SP, Campoli-Richards DM.  
Omeprazole - a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome.  
Drugs 1986;32:15-47.
8. Ekman L, Hansson E, et al.  
Toxicological studies on omeprazole.  
Scand J Gastroenterol 1985;20(108):53-69.
9. Hameeteman W, Tytgat GN.  
Healing of chronic Barrett ulcers with omeprazole.  
Am J Gastroenterol 1986;81:764-766.
10. Howden CW, Payton CD, et al.  
Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure.  
Eur J Clin Pharmacol 1985;28:637-640.

11. Labenz J, Ruhl GH, Bertrams J, Borsch G.  
Medium- or high-dose omeprazole plus amoxicillin eradicates *Helicobacter pylori* in gastric ulcer disease.  
*Am J Gastroent* 1994;89(5):726-730.
12. Lamberts R, et al.  
Long-term omeprazole treatment in man. Effects on gastric endocrine cell population.  
*Digestion* 1988;39:126-135.
13. Lloyd-Davies KA, et al.  
Omeprazole in the treatment of ZES: a 4 year international study.  
*Alimentary Pharmacol and Ther* 1988;2:13-32.
14. Logan RPH, Bardhan KD, et al.  
Eradication of *Helicobacter pylori* and prevention of recurrence of duodenal ulcer: a randomized, double-blind, multi-centre trial of omeprazole with or without clarithromycin.  
*Aliment Pharmacol Ther* 1995;9:417-423.
15. McArthur KE, Collen MJ, et al.  
Omeprazole: Effective, convenient therapy for Zollinger-Ellison Syndrome.  
*Gastroenterology* 1985;88:939-944.
16. Regardh CG, Gabrielsson M, et al.  
Pharmacokinetics and metabolism of omeprazole in animals and man - an overview.  
*Scand J Gastroenterol* 1985;20(108):79-94.
17. Wallmark B, Lindberg P.  
Mechanism of action of omeprazole.  
*ISI Atlas of Science: Pharmacology* 1987;1:158-160.