OMEPRAZOLE
Losec®

10mg and 20mg Capsules
Acid Pump Inhibitors

FORMULATION
Each capsule contains Omeprazole 10 mg or 20 mg.

PHARMACEUTICAL FORM
Omeprazole (LOSEC) capsule 10 mg: hard gelatin capsule with an opaque pink body, marked 10 and an opaque pink cap marked A/OS. Each capsule contains omeprazole 10 mg as enteric coated pellets.

Omeprazole (LOSEC) capsule 20 mg: hard gelatin capsule with an opaque pink body, marked 20 and an opaque reddish-brown cap marked A/OM. Each capsule contains omeprazole 20 mg as enteric-coated pellets.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Omeprazole, a racemic mixture of two active enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Site and mechanism of action:
Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+, K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion:
Oral dosing with Omeprazole (Losec) once daily provides for rapid and effective inhibition of daytime and nighttime gastric acid secretion with maximum effect being achieved within 4 days
of treatment. With Omeprazole (LOSEC) 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% twenty four hours after dosing.

Oral dosing with Omeprazole (LOSEC) 20 mg maintains an intragastric pH of ≥3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. No tachyphylaxis has been observed during treatment with omeprazole.

**Effect on Helicobacter pylori:**
*Helicobacter pylori* is associated with acid peptic disease, including duodenal and gastric ulcer disease, in which about 95% and 70% of patients respectively are infected with this bacterium. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer. Eradication of *H. pylori* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment. Eradication of *H. pylori* with omeprazole and antimicrobials is also associated with regression of atrophic gastritis, and a reduced risk for development of gastric cancer.

**Other effects related to acid inhibition:**
During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

**Pharmacokinetic properties**

**Absorption and distribution:**
Omeprazole is acid labile and is therefore administered orally as enteric-coated granules in capsules. Absorption takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiency. In elderly and in patients with
hepatic insufficiency, the volume of distribution is slightly decreased. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

**Metabolism and excretion:**
The plasma elimination half-life of omeprazole is usually shorter than one hour and there is no change in half-life during long-term treatment. Omeprazole is completely metabolized by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. In accordance with this, as a consequence of competitive inhibition, there is a potential for metabolic drug-drug interactions between omeprazole and other substrates for CYP2C19.

Results from a range of interaction studies with Omeprazole (Losec) versus other drugs indicate however that omeprazole, 20 - 40 mg daily, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lidocaine, quinidine, estradiol, erythromycin, budesonide).

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an orally given dose is excreted as metabolites in the urine, and the remainder is found in the feces, primarily originating from bile secretion.

The systemic bioavailability and elimination of omeprazole is unchanged in patients with reduced renal function. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but omeprazole has not shown any tendency to accumulate with once daily dosing.

**Children:**
Available data from children (1 year and older) suggests that the pharmacokinetics, within the recommended dosages, is similar to those reported in adults.

**PRECLINICAL SAFETY DATA**
Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from direct effect of any individual drug.

**THERAPEUTIC INDICATION**
Omeprazole (LOSEC) is indicated for the treatment of
- Duodenal ulcer
- Gastric ulcer
- NSAID associated gastric and duodenal ulcers or erosions
- Helicobacter pylori eradication in peptic ulcer disease
- Reflux esophagitis
- Symptomatic gastro-esophageal reflux disease
- Acid related dyspepsia
- Zollinger-Ellison syndrome
- Patients considered to be at risk of aspiration of gastric contents during general anesthesia/Acid aspiration prophylaxis.

**DOSAGE AND ADMINISTRATION**

Omeprazole (LOSEC) capsules are recommended to be given in the morning and swallowed whole with half a glass of water. The capsules must not be chewed or crushed

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food

The capsule can be opened and the contents swallowed directly with half a glass of water or after mixing the contents in a slightly acidic fluid eg, fruit juice or applesauce, or in non-carbonated water. The dispersion should be taken immediately (or within 30 minutes). Always stir just before drinking. Rinse it down with half a glass of water.

Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. Ingest without chewing the enteric-coated pellets.

*Duodenal ulcer:*
The recommended dosage in patients with an active duodenal ulcer is Omeprazole (LOSEC) 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 weeks’ treatment period.

In patients with poorly responsive duodenal ulcer, 2 capsules of Omeprazole (LOSEC) 20 mg once daily is recommended and healing is usually achieved within 4 weeks.

For the prevention of relapse in patients with duodenal ulcer disease the recommended dose is Omeprazole (LOSEC) 10 mg once daily. If needed the dose can be increased to 1 to 2 capsules of Omeprazole (LOSEC) 20 mg once daily.

For NSAID associated duodenal ulcers see *NSAID associated gastroduodenal lesions.*

For eradication of *Helicobacter pylori* see *Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease.*

*Gastric ulcer:*
The recommended dosage is Omeprazole (LOSEC) 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.
In patients with poorly responsive gastric ulcer, 2 capsules of Omeprazole (LOSEC) 20 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the prevention of relapse of patients with poorly responsive gastric ulcer, the recommended dose is Omeprazole (LOSEC) 20 mg once daily. If needed the dose may be increased to 2 capsules of Omeprazole (LOSEC) 20 mg once daily.

For eradication of *Helicobacter pylori* see *Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease*.

For NSAID associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients with or without continued NSAID treatment the recommended dosage of Omeprazole (LOSEC) is 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4-week treatment period.

For the prevention of NSAID associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms the recommended dosage of Omeprazole (LOSEC) is 20 mg once daily.

*Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease:*

Triple therapy regimens:
Omeprazole (LOSEC) 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice a day for one week. or

Omeprazole (LOSEC) 20 mg, clarithromycin 250 mg and metronidazole 500 mg (or tinidazole 500 mg), all twice a day for one week. or

Omeprazole (LOSEC) 20 mg 2 capsules once daily with amoxicillin 500 mg and metronidazole 500 mg both three times a day for one week.

Dual therapy regimens:
Omeprazole (LOSEC) 40-80 mg daily with amoxicillin 1.5 g daily in divided doses for two weeks. In clinical studies daily doses of 1.5-3 g of amoxicillin have been used. Or

Omeprazole (LOSEC) 20 mg 2 capsules once daily and clarithromycin 500 mg three times a day for two weeks.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for *Duodenal* and *Gastric* ulcer.

In each regimen if the patient is still *Hp* positive, therapy may be repeated.
Reflux esophagitis:
The recommended dosage is Omeprazole (LOSEC) 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4-week treatment period.

In patients with severe reflux esophagitis 2 capsules of Omeprazole (LOSEC) 20 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the long-term management of patients with healed reflux esophagitis the recommended dose is Omeprazole (LOSEC) 10 mg once daily. If needed the dose may be increased to Omeprazole (LOSEC) 20-40 mg once daily.

Severe reflux esophagitis in children from one year and older:
The recommended dosage regimen for healing is:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20 kg</td>
<td>Losec 10mg once daily</td>
</tr>
<tr>
<td>&gt; 20 kg</td>
<td>Losec 20mg once daily</td>
</tr>
</tbody>
</table>

Symptomatic gastro-esophageal reflux disease: The recommended dosage is Omeprazole (LOSEC) 20 mg daily. Symptom relief is rapid. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should be considered.

If symptom control has not been achieved after 4 weeks of treatment with Omeprazole (LOSEC) 20 mg daily, further investigation is recommended.

Acid-related dyspepsia: In the relief of symptoms in patients with epigastric pain/discomfort with or without heartburn the recommended dosage is Omeprazole (Losec) 20 mg once daily. Patients may respond adequately to 10 mg daily and therefore this dose could be considered as a starting dose.

If symptom control has not been achieved after 4 weeks of treatment with Omeprazole (Losec) 20 mg daily, further investigation is recommended.

Zollinger-Ellison syndrome:
In patients with Zollinger-Ellison syndrome, the dosage should be individually adjusted and treatment continued as long as is clinically indicated. The recommended initial dosage is 3 capsules of Omeprazole (LOSEC) 20 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of Omeprazole (LOSEC) 20-120 mg daily. When doses exceed Omeprazole (LOSEC) 80 mg daily, the dose should be divided and given twice daily.

Acid aspiration prophylaxis:
The recommended dosage is 2 capsules of Omeprazole (LOSEC) 20 mg in the evening before surgery, followed by 2 capsules of Omeprazole (LOSEC) 20 mg on the morning after surgery.
**Impaired renal function:**
Dose adjustment is not needed in patients with impaired renal function.

**Impaired hepatic function:**
As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function a daily dose of 10-20 mg may be sufficient.

**Elderly:** Dose adjustment is not needed in the elderly.

**CONTRAINDICATIONS**
Known hypersensitivity to omeprazole.

**SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melena) and when gastric ulcer is suspected or present, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.

**INTERACTIONS**
The absorption of some drugs might be altered due to the increased intragastric acidity. Thus it can be predicted that the absorption of ketoconazole will decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

No interaction with food or concomitantly administered antacids has been found.

As omeprazole is metabolised in the liver through cytochrome P450 2C19 (CYP2C19), it can prolong the elimination of diazepam, phenytoin, warfarin (R - warfarin) and other vitamin K antagonists, which are in part substrates for this enzyme.

Monitoring of patients receiving phenytoin, is recommended and a reduction of the phenytoin dose may be necessary. However, concomitant treatment with LOSEC 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this drug. In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with Omeprazole (LOSEC) 20 mg daily did, however, not change coagulation time in patients on continuous treatment with warfarin.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration but there is no interaction with metronidazole or amoxicillin. These antimicrobials are used together with omeprazole for eradication of *Helicobacter pylori*.

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.
Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. However, a dose adjustment of omeprazole is not required.

**PREGNANCY AND LACTATION**

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the fetus/newborn child. Omeprazole (LOSEC) can be used during pregnancy. Omeprazole is excreted in the breast milk but is not likely to influence the child when therapeutic doses are used.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Omeprazole (LOSEC) is not likely to affect the ability to drive or use machines.

**UNDESIRABLE EFFECTS**

Omeprazole (LOSEC) is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use, but in many cases a relationship to treatment with omeprazole has not been established.

The following definitions of frequencies are used:

- **Common** >1/100
- **Uncommon** >1/1000 and <1/100
- **Rare** <1/1000

**Common**

- **Central and peripheral nervous system:** Headache
- **Gastrointestinal:** Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence

**Uncommon**

- **Central and peripheral nervous system:** Dizziness, paraesthesia, somnolence, insomnia and vertigo.
- **Hepatic:** Increased liver enzymes.
- **Skin:** Rash, dermatitis and/or pruritus, Urticaria.
- **Other:** Malaise.
Rare

Central and peripheral nervous system:
Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.

Endocrine
Gynaecomastia.

Gastrointestinal
Dry mouth, stomatitis and gastrointestinal candidiasis.

Haematological
Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

Hepatic
Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure.

Musculoskeletal
Arthralgia, muscular weakness and myalgia.

Skin
Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia.

Other
Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock.
Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

OVERDOSAGE
Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhea and headache have been reported from overdose with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment has been needed.
CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

STORAGE
Store at a temperature not exceeding 30°C

AVAILABILITY
Box of 14's

Validity Code
Based on CDS Gl.000-002-604.9.0
Dated June 2006
Phil Specific Text GEL Loc 06/JF/PH/Gl.000-051-922.3.0

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