# Omeprazole 40 mg powder and solvent for solution for injection and Losec 40 mg powder for solution for infusion

## Core Safety Profile

## 4.2 Posology and method of administration

Special populations

*Impaired renal function*

Dose adjustment is not needed in patients with impaired renal function (see section 5.2).

*Impaired hepatic function*

In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient (see section 5.2).

*Elderly (> 65 years old)*

Dose adjustment is not needed in the elderly (see section 5.2).

*Paediatric patients*

There is limited experience with Losec for intravenous use in children.

## 4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients.

Omeprazole like other proton pump inhibitors must not be used concomitantly with nelfinavir (see section 4.5).

## 4.4 Special warnings and special precautions for use

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

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin $B_{12}$ (cyanocobalamin) due to hypo- or achlorhydria. This should

be considered in patients with reduced body stores or risk factors for reduced vitamin $B_{12}$ absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Text applies to Losec oral Rx and i v formulations

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Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

*Interference with laboratory tests*
Increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances

*Active substances with pH dependent absorption*
The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

*Nelfinavir, atazanavir*
The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). Co-administration of omeprazole (40 mg once daily) reduced mean nelvinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75-90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

*Digoxin*
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

*Clopidogrel*
In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered 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 it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from

observational and clinical studies.

*Other active substances*
The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Active substances *metabolised by CYP2C19*
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

*Cilostazol*
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased $C_{max}$ and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

*Phenytoin*
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism

*Saquinavir*
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

*Tacrolimus*
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

*Methotrexate*
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

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Effects of other active substances on the pharmacokinetics of omeprazole

*Inhibitors of CYP2C19 and/or CYP3A4*
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

*Inducers of CYP2C19 and/or CYP3A4*
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

## 4.6 Pregnancy and lactation

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

## 4.7 Effects on ability to drive and use machines

Losec is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

## 4.8 Undesirable effects

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

| **SOC/frequency** | **Adverse reaction** |
|---|---|
| **Blood and lymphatic system disorders** | |
| Rare: | Leukopenia, thrombocytopenia |

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|---|---|---|
| Rare: | Leukopenia, thrombocytopenia | |
| Very rare: | Agranulocytosis, pancytopenia | |
| **Immune system disorders** | | |
| Rare: | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock | |
| **Metabolism and nutrition disorders** | | |
| Rare: | Hyponatraemia | NL/H/2081/001 006,008,010/IB/008 IT/254/H/001-004/1B/ 008 |
| Not known | Hypomagnesaemia | |
| **Psychiatric disorders** | | |
| Uncommon: | Insomnia | |
| Rare: | Agitation, confusion, depression | |
| Very rare: | Aggression, hallucinations | |
| **Nervous system disorders** | | |
| Common: | Headache | |
| Uncommon: | Dizziness, paraesthesia, somnolence | |
| Rare: | Taste disturbance | |
| **Eye disorders** | | |
| Rare: | Blurred vision | |
| **Ear and labyrinth disorders** | | |
| Uncommon: | Vertigo | |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Rare: | Bronchospasm | |
| **Gastrointestinal disorders** | | |
| Common: | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting | |
| Rare: | Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis | NL/H/2081/001-010/II/006 IT/H/254/001-004/II/006 |
| **Hepatobiliary disorders** | | |
| Uncommon: | Increased liver enzymes | |
| Rare: | Hepatitis with or without jaundice | |
| Very rare: | Hepatic failure, encephalopathy in patients with pre-existing liver disease | |
| **Skin and subcutaneous tissue disorders** | | |
| Uncommon: | Dermatitis, pruritus, rash, urticaria | |
| Rare: | Alopecia, photosensitivity | |
| Very rare: | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) | |
| **Musculoskeletal and connective tissue disorders** | | |
| Uncommon: | Fracture of the hip, wrist or spine | NL/H/2081/001 006,008,010/IB/008 IT/254/H/001-004/1B/ 008 |
| Rare: | Arthralgia, myalgia | |
| Very rare: | Muscular weakness | |
| **Renal and urinary disorders** | | |
| Rare: | Interstitial nephritis | |
| **Reproductive system and breast disorders** | | |
| Very rare: | Gynaecomastia | |
| **General disorders and administration site conditions** | | |
| Uncommon: | Malaise, peripheral oedema | |

| | |
|---|---|
| Rare: | Increased sweating |

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole intravenous injection, especially at high doses, but no causal relationship has been established.

## 4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole in humans. 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 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

Intravenous doses of up to 270 mg on a single day and up to 650 mg over a three-day period have been given in clinical trials without any dose-related adverse reactions.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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*.

Chromogranin A (CgA) also increases due to decreased gastric acidity. This CgA modifying effect cannot be demonstrated five days after stopping treatment with PPIs.