# SUMMARY OF PRODUCT CHARACTERISTICS
# LOSEC®

## 1. NAME OF THE MEDICINAL PRODUCT

**LOSEC® 20 mg**
**LOSEC® 20 mg Rx**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg omeprazole.
Excipients with known effect: each capsule contains 8 mg lactose and 0.25 mg sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant hard gelatin capsules.
Hard gelatine capsules with an opaque pink body marked 20 and an opaque reddish-brown cap marked "A LOSEC®" in black ink. Each capsule contains white to slightly beige enteric-coated pellets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Acute duodenal ulcer.
- Acute gastric ulcer.
- *Helicobacter pylori*-associated peptic ulcer disease in combination with antibiotics.
- Reflux esophagitis:
  - Treatment
  - Long-term management
  - Maintenance treatment for the prevention of relapse in patients with severe reflux esophagitis
- Treatment of severe reflux oesophagitis in children from one year of age and older
- Maintenance treatment for the prevention of relapse in patients with poorly responsive peptic ulcer.
- Zollinger-Ellison syndrome.
- Treatment and prevention of NSAID-associated duodenal and gastric ulcers or erosions in high risk patients.
- Losec 20 mg (OTC): Relief of reflux-like symptoms (e.g. heartburn) with frequency of two or more days a week in sufferers aged 18 and over.

## 4.2 Posology and method of administration

**Posology**

***Adults***

Acute Duodenal Ulcer

The recommended dosage is 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 duodenal ulcer, Losec 40 mg once daily is recommended and healing is usually achieved within 4 weeks.

The effectiveness of Losec is not affected by concomitant NSAID treatment and the usual duration of treatment is recommended.

Maintenance Treatment for the Prevention of Relapse in Patients with Poorly Responsive Peptic Ulcer

For the prevention of relapse in patients with poorly responsive peptic ulcer,20 mg Losec once daily is recommended. In case of recurrence, the dose can be increased to 40 mg Losec once daily.

Acute Gastric Ulcer

The recommended dosage is 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, 40 mg Losec once daily is recommended and healing is usually achieved within eight weeks.

The effectiveness of Losec is not affected by concomitant NSAID treatment and the usual duration of treatment is recommended.

Helicobacter Pylori-Associated in peptic ulcer disease

The recommended alternative treatment regimens for eradication of *H pylori* are:

*Triple Therapy Regimen*

This involves three alternatives:

1. Losec 20 mg , amoxicillin 1 g, and clarithromycin 500 mg, all twice a day for 1 week.
2. Losec 20 mg clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg), all twice a day for 1 week.
3. Losec 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg, both 3 times a day for 1 week.

*Dual Therapy Regimen*

Losec 40-80 mg daily with amoxicillin 2 g daily in divided doses for two weeks. In clinical studies daily doses of 1.5-3 g of amoxicillin have been used, with or without addition of metronidazole 400 mg t.i.d.

To ensure healing in patients with active peptic ulcer disease refer to dosage recommendations for duodenal and gastric ulcer.

In each regimen, if the patient is still H. pylori positive, therapy may be repeated.

NSAID-Associated Duodenal Ulcers, Gastric Ulcers, or Gastroduodenal Erosions in Patients with or without Continued NSAID Treatment

*Treatment*: the recommended dosage is 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 four weeks treatment period.

*Prevention:* For the prevention of NSAID-associated duodenal ulcers, gastric ulcers, gastroduodenal erosions, and dyspeptic symptoms, the recommended dosage of Losec is 20 mg once daily.

Reflux Esophagitis

*Treatment*

In patients with reflux esophagitis, the recommended dose is Losec 20 mg once daily given for 4 weeks. For those patients not fully healed after the initial course, healing usually occurs during a further four weeks treatment. Losec has also been used in a dose of 40 mg once daily in patients with reflux esophagitis refractory to other therapy. Healing usually occurred within 8 weeks.

*Long-Term Management*

For the long-term management of patients with healed reflux oesophagitis the recommended dose is 10 mg of omeprazole once daily. If needed, the dose can be increased to Losec 20-40 mg once daily.

*Maintenance Treatment for the Prevention of Relapse in Patients with Severe Reflux Esophagitis*

For the prevention of relapse in patients with severe reflux esophagitis, 20 mg Losec once daily is recommended. In case of recurrence, the dose can be increased to 40 mg Losec once daily.

Zollinger-Ellison Syndrome

The recommended initial dosage is 60 mg Losec once daily. The dosage should be adjusted individually and treatment continued as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

***Paediatric population***

*Severe Reflux Esophagitis in Children* ***from One Year of Age and Older*** *and ≥ 10kg*

The recommended dosage regimen for healing is as follows:

| Age | Weight | Dosage |
|---|---|---|
| ≥ 1 year of age | 10-20 kg body weight | Omeprazole 10 mg once daily, which may be increased to 20 mg if needed. |
| | Over 20 kg body weight | Losec 20 mg once daily, which may be increased to 40 mg if needed. |

***Special populations***

**Use in the Elderly**

No dosage adjustment is necessary in the elderly (see section 5.2).

**Hepatic impairment**

Use in Patients with impaired hepatic function: as bioavailability and half-life can increase in patients with impaired hepatic function, the dose requires adjustment with a maximum daily dose of 20 mg.

**Renal impairment**

Use in Patients with impaired renal function: dose adjustment is not required in patients with impaired renal function (see section 5.2).

**Method of administration**

Losec capsules should be taken before meals, and are recommended to be given in the morning and swallowed whole with liquid.

**For patients with swallowing difficulties** the capsule might be opened and the contents swallowed or suspended in a slightly acidic fluid e.g. fruit juice, yoghurt soured milk, or in non-carbonated water. The suspended contents should be taken within 30 minutes.

Alternatively these patients can suck the capsule and swallow the contents. The enteric-coated pellets must not be chewed.

**For children who are unable to swallow** the capsule whole, or swallow the contents of the opened capsule, or suck the capsule and swallow its contents, Losec must only be administered by opening the capsules and suspending its contents in a slightly acidic fluid as directed above.

## 4.3 Contraindications

Hypersensitivity to the active substance substituted benzimidazoles or to any of the excipients listed in section 6.1.

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

## 4.4 Special warnings and 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 .

*Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely and rarely, respectively in association with omeprazole treatment.*

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.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Losec.

SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

**Interference with laboratory tests**

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 14 days before CgA measurements (see section 5.1). Healthcare providers should temporarily stop omeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

**Losec contains lactose**. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
**Losec contains less than 1 mmol sodium** (23 mg) per capsule, that is to say essentially 'sodium-free'.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also Clostridium difficile (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 Nelfinavir 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*

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between Clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and Clopidogrel should be discouraged (see section 4.4).

*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.

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 Fertility, Pregnancy and lactation

Pregnancy
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.

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

Fertility
Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

## 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

Summary of the safety profile

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

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with omeprazole treatment (see section 4.4).

Tabulated list of adverse reactions

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 |
| Very rare: | Agranulocytosis, pancytopenia |
| **Immune system disorders** | |
| Rare: | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock |
| **Metabolism and nutrition disorders** | |
| Rare: | Hyponatraemia |
| Not known: | Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia<br>Hypomagnesaemia may also be associated with hypokalaemia. |

| | |
|---|---|
| **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, fundic gland polyps (benign) |
| Rare: | Dry mouth, stomatitis, gastrointestinal candidiasis |
| Not known | Microscopic colitis |
| **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, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) |
| Very rare: | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) |
| Not known: | Subacute cutaneous lupus erythematosus (see section 4.4). |
| **Musculoskeletal and connective tissue disorders** | |
| Uncommon | Fracture of the hip, wrist or spine |
| 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 |

Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: **https://sideeffects.health.gov.il**

## 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 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.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, Proton pump inhibitors, ATC code: A02BC01

Mechanism of action
Omeprazole, a racemic mixture of two 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.

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.

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

*Effect on gastric acid secretion*
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 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% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of $\geq 3$ 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 oesophagus in patients with gastro-oesophageal 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 H. pylori*
*H. pylori* is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *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 high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

*Other effects related to acid inhibition*
During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a 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* and, in hospitalised patients, possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

Paediatric population
In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90% of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0–24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of the dose.

*Eradication of H. pylori in children*
A randomised, double blind clinical study (Héliot study) concluded that omeprazole, in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis: *H. pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

## 5.2 Pharmacokinetic properties

Absorption
Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution
The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Biotransformation
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

**Linearity/non-linearity**
The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone).

No metabolite has been found to have any effect on gastric acid secretion.

**Special populations**

Hepatic impairment
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once-daily dosing.

Renal impairment
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

Paediatric population

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

### 5.3 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 $H_2$-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content:
Mannitol, methacrylic acid copolymer, lactose anhydrous, hydroxypropylmethyl cellulose (hypromellose), hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, disodium phosphate dihydrate, sodium lauril sulfate, magnesium stearate.

Capsule shell:
Gelatine, red iron oxide, titanium dioxide, water.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
This medicine may be used for 3 months following first opening of the bottle without exceeding the expiry date printed on packaging materials.

### 6.4 Special precautions for storage

Store in a dry place below 25°C.
Keep the container tightly closed. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

Losec Capsules are provided in high-density polyethylene bottles with lids containing integral desiccant.

Packs of 7, 14, 28 or 30 capsules. Not all pack sizes may be marketed.

## 7. LICENSE HOLDER & MANUFACTURER

Teva Israel Ltd.,124 Dvora HaNevia St. 6944020 Tel-Aviv.

## 8. REGISTRATION NUMBERS

Losec 20 mg Rx Capsules: 050.66.26256

Losec 20 mg Capsules (OTC): 139.78.31879

**This leaflet was revised in July 2022 in accordance with the Ministry of Health guidelines.**