PROPOSED PI FOR SANDOZ OMEPRAZOLE 20

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

SANDOZ OMEPRAZOLE 20 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Sandoz Omeprazole 20 capsule contains 20 mg omeprazole in a gastro-resistant formulation.

Contains sugar (sucrose 108,04 mg) and mannitol 7,91 mg.

3. PHARMACEUTICAL FORM

A capsule with opaque yellow body and cap, containing off-white to cream-white spherical pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SANDOZ OMEPRAZOLE 20 is indicated in:

Adults*:*

- Treatment of duodenal ulcer, including prevention of relapse, gastric ulcer, and reflux oesophagitis.
- Long-term management of reflux oesophagitis, and Zollinger-Ellison syndrome.

- Symptomatic relief of heartburn in patients with gastro-oesophageal reflux disease (GORD) and the short-term relief of functional dyspepsia.
- *Helicobacter pylori*-positive duodenal ulcers, as part of an eradication program with appropriate antibiotics.
- Treatment of non-steroidal anti-inflammatory drugs (NSAIDs)-associated gastric and/or duodenal ulcers and erosions.
- Reduction of the risk to develop gastric and/or duodenal ulcer/erosions, and reduction of the risk of relapse for previously healed gastric and/or duodenal ulcer/erosions in patients on NSAIDs treatment.

Children*:*

Short-term (up to 3 months) treatment of severe ulcerative reflux oesophagitis resistant to previous medical treatment.

4.2 Posology and method of administration

SANDOZ OMEPRAZOLE 20 is recommended to be given in the morning and swallowed whole with a half glass of liquid. The SANDOZ OMEPRAZOLE 20 capsules should not be chewed or crushed.

The recommended dosages for adults are:

Duodenal ulcer*:*

20 mg once daily for 2 to 4 weeks. In some duodenal ulcer patient's refractory to other treatment regimens, 40 mg once daily may be effective.

Prevention of relapse in patients with duodenal ulcer*:*

10 mg once daily. If necessary, the dose can be increased up to 20 to 40 mg once daily. The above recommended dosage regimens are inclusive of *Helicobacter pylori*-positive duodenal ulcers as part of the eradication program with appropriate antibiotics.

Gastric ulcer and reflux oesophagitis:

20 mg once daily for 4 to 8 weeks. In some gastric ulcer and reflux oesophagitis patient's refractory to other treatment regimens, 40 mg once daily may be effective.

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

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with SANDOZ OMEPRAZOLE 20 at a dosage of 20 mg once daily.

NSAIDS-associated gastroduodenal lesions with or without continued NSAID treatment:

20 mg once daily. In most patients healing occurs within 4 weeks. For patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks of treatment.

Prevention of NSAIDs-associated gastroduodenal lesions and dyspeptic symptoms:

20 mg once daily.

Symptomatic gastroesophageal reflux disease:

20 mg once daily. Patients may respond adequately to 10 mg daily, therefore individual dose adjustments should be considered. If symptom control has not been achieved after 4 weeks of treatment with 20 mg daily, further investigation is recommended.

Zollinger-Ellison syndrome:

60 mg once daily. The dosage should be adjusted individually and treatment continued as long as clinically indicated. With doses above 80 mg daily, the dose should be divided and given twice daily.

The recommended dosages for children are:

There is very limited experience with the use of SANDOZ OMEPRAZOLE 20 in children (see "WARNINGS AND SPECIAL PRECAUTIONS").

Severe ulcerative reflux oesophagitis in children from one year and older:

Weight:	***Dosage:***
10 to 20 kg	10 mg once daily. If needed increase to 20 mg once daily.
> 20 kg	20 mg once daily. If needed increase to 40 mg once daily.

Special populations

Elderly:

Dose reductions are not necessary in elderly patients. The long-term safety of SANDOZ OMEPRAZOLE 20 in patients with renal and/or hepatic impairment has not been established (see "WARNINGS AND SPECIAL PRECAUTIONS").

Impaired hepatic function:

Bioavailability and plasma half-life of SANDOZ OMEPRAZOLE 20 are increased in patients with impaired hepatic function, therefore a daily dose of 10 to 20 mg is generally sufficient.

4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients listed in section 6.1.

Safety in pregnancy and lactation has not been established.

SANDOZ OMEPRAZOLE 20 should not be administered with St John's Wort (see section 4.5).

SANDOZ OMEPRAZOLE 20 must not be used concomitantly with nelfinavir or atazanavir (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 melaena) and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with SANDOZ OMEPRAZOLE 20 may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5).

Hepatic impairment may require a reduction in dose (see section 4.2).

SANDOZ OMEPRAZOLE 20, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypohydria/ 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 SANDOZ OMEPRAZOLE 20, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and SANDOZ OMEPRAZOLE 20 (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of SANDOZ OMEPRAZOLE 20 and clopidogrel should be avoided.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like SANDOZ OMEPRAZOLE 20 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 proton pump inhibitor.

For patients expected to be on prolonged treatment or who take SANDOZ OMEPRAZOLE 20 with digoxin or medicinal products that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting SANDOZ OMEPRAZOLE 20 treatment and periodically during treatment.

SANDOZ OMEPRAZOLE, 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.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue SANDOZ OMEPRAZOLE and evaluate patients with suspected acute TIN.

During long-term treatment, gastric glandular cysts have been reported in increased frequency. These physiological changes result from pronounced inhibition of gastric acid secretion.

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 SANDOZ OMEPRAZOLE 20. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with SANDOZ OMEPRAZOLE 20.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, SANDOZ OMEPRAZOLE 20 treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have

not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of SANDOZ OMEPRAZOLE 20 treatment.

Treatment with SANDOZ OMEPRAZOLE may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile (see section 5.1).

There is very limited experience with the use of SANDOZ OMEPRAZOLE 20 in children.

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

The long-term safety of SANDOZ OMEPRAZOLE 20 in patients with renal and/or hepatic impairment has not been established.

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

Sucrose:

SANDOZ OMEPRAZOLE 20 contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take SANDOZ OMEPRAZOLE 20.

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines 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 SANDOZ OMEPRAZOLE 20 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 SANDOZ OMEPRAZOLE 20.

Concomitant administration of SANDOZ OMEPRAZOLE 20 with nelfinavir is contraindicated (see section 4.3). Co-administration of SANDOZ OMEPRAZOLE 20 (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 to 90 %. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of SANDOZ OMEPRAZOLE 20 with atazanavir is contraindicated (see section 4.3).

Concomitant administration of SANDOZ OMEPRAZOLE 20 (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 SANDOZ OMEPRAZOLE 20 (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been ~~rarely~~ reported. Caution should be exercised when SANDOZ OMEPRAZOLE 20 is given at high doses in elderly patients. Therapeutic medicinal monitoring of digoxin should 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, at the same time as clopidogrel).

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. The consequence of this would be a reduction in the antiplatelet activity of clopidogrel, which may predispose to an increase in cardiovascular events. As a precaution, concomitant use of omeprazole and clopidogrel should be avoided (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

SANDOZ OMEPRAZOLE 20 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 medicines are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin. Monitoring of INR is recommended and dosage reductions may be necessary when SANDOZ OMEPRAZOLE 20 is given concomitantly.

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 SANDOZ OMEPRAZOLE 20 treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending SANDOZ OMEPRAZOLE 20 treatment.

There may be interactions with other medicines that are also metabolised via the cytochrome P450 enzyme system.

Unknown mechanism

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70 % for saquinavir. Caution is advised with concomitant use of saquinavir/ritonavir.

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 SANDOZ OMEPRAZOLE 20 may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since SANDOZ OMEPRAZOLE 20 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 SANDOZ OMEPRAZOLE 20 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 and should not be used concomitantly with SANDOZ OMEPRAZOLE 20.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see "CONTRAINDICATIONS").

SANDOZ OMEPRAZOLE 20 is excreted in breast milk.

4.7 Effects on ability to drive and use machines

SANDOZ OMEPRAZOLE 20 may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressant agents. Patients should be advised, particularly at the initiation of therapy, against driving of

vehicles or operating machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Summary of the safety profile

The most frequent undesirable effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Blood and lymphatic system disorders

Less frequent: Pancytopenia, thrombocytopenia, agranulocytosis, leucopenia

Immune system disorders

Less frequent: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Less frequent: Hyponatraemia

Frequency unknown: Hypomagnesaemia Severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

Psychiatric disorders

Less frequent: Confusion, aggression, hallucinations, insomnia and parasthaesias have occurred, predominantly in severely ill patients, agitation

Nervous system disorders

Frequent: Headache (severe enough to require discontinuation of therapy in some cases)

Less frequent*:* Taste disturbances, paraesthaesia, dizziness and somnolence

Eye Disorders

Less frequent: Blurred vision

Ear and labyrinth disorders

Less *Frequent:* Vertigo

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm

Gastrointestinal disorders

Frequent: Diarrhoea (severe enough to require discontinuation of therapy in some cases), constipation, nausea, vomiting, flatulence, abdominal pain or colic, fundic gland polyps (benign)

Less frequent: Dry mouth, stomatitis, gastrointestinal candidiasis, acid regurgitation and increased gastro-intestinal bacteria

Frequency unknown: Microscopic colitis

Hepatobiliary disorders

Less frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease.

Skin and subcutaneous tissue disorders

Less frequent: Photosensitivity, bullous eruption, erythema multiforme, pruritus dermatitis, skin rash and itching, urticaria, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, alopecia

Frequency unknown: Subacute cutaneous lupus erythematosus (see section 4.4)

Musculoskeletal and connective tissue disorders

Less frequent: Asthenia, arthralgia, myalgia, fracture of the hip, wrist or spine, muscular weakness

Renal and urinary disorders

Less frequent: Interstitial nephritis (may progress to acute kidney injury and/or chronic renal failure and symptoms of interstitial nephritis may persist even when treatment with PPI is terminated).

Reproductive system and breast disorders

Less frequent: Gynaecomastia

General disorders and administration site conditions

Less frequent*:* Increased sweating, peripheral oedema, malaise

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 2400 mg omeprazole (120 times the usual recommended clinical dose).

Blurred vision, diaphoresis, flushing, headache, malaise, nausea, vomiting, dizziness, abdominal pain, diarrhoea and tachycardia have been reported. Also apathy, depression and confusion have been described in single cases.

There is no specific antidote for overdose with omeprazole. Treatment is symptomatic and supportive. Due to extensive protein binding, omeprazole is not readily dialysable. Patients in whom overdose is confirmed or suspected should be referred for a consultation with a medical practitioner/doctor.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 11.4.3 Medicines acting on the gastrointestinal tract – Other, ATC code: A02BC01

5.1 Pharmacodynamic properties

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.

Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

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 ≥ 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/normalises acid exposure of the oesophagus in patients with gastroesophageal 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 medicinal products may lead to slightly increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* 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 gastroesophageal 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

Orally administered omeprazole is well absorbed but to a variable extent. 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 to 6 hours. Concomitant intake of food has no influence on the bioavailability of omeprazole. The systemic availability (bioavailability), from a single oral dose of omeprazole (depends on dose and gastric pH) 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 more than 97 % plasma protein bound.

Biotransformation

Clearance from the circulation is by hepatic metabolism, with a plasma half-life of 30 to 90 minutes. 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 sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic medicine-medicine 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 average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in plasma half-life during treatment. 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 remaining 20 % in the faeces, primarily originating from bile secretion.

Linearity/non-linearity

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) and not to the actual plasma concentration at a given time. 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 sulphone).

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 people

The metabolism rate of omeprazole is somewhat reduced in the elderly (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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate, Eudragit L30-D55, hydroxypropyl methyl cellulose, mannitol, neutral pellets (maize starch, sucrose), polyethylene glycol 6000, polysorbate 80, sodium lauryl sulphate, talc, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store tightly closed, at or below 25 °C. Protect from light and moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Packs of 15, 28, 30 or 50 capsules in white, tamper evident, plastic containers.

Packs of 15, 28, 30 or 50 capsules in Aluminium/Aluminium blisters.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West,

Waterfall City,

Jukskei View,

Midrand,

2090

8. REGISTRATION NUMBER(S)

36/11.4.3/0430

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2012

10. DATE OF REVISION OF THE TEXT

21 September 2022

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Sandoz Omeprazole 20	NS2	04/11.4.3/1715

Name and address of manufacturer:

Liconsa, Liberación Controlada de Sustancias Activas S.A.

Avda, Miralcampo, N° 7,

Poligono Industrial Miralcampo

19200 Azuqueca de Henares (Guadalajara)

Spain

[1]Company Reg. No.: 1990/001979/07

References:

Ref. No	Description	Module
1	Current UK approved innovator SmPC: Losec Capsules 20 mg, Neon Healthcare Ltd, UK, 16 May 2022	1.3.1.2
2	Safety issue, SAHPRA communication, proton pump inhibitors-possible risk of myocardial infarction, 06 May 2020	1.3.1.2
3	Safety issue, SAHPRA communication, Proton Pump Inhibitors - increased risk of subclinical acute interstitial nephritis associated with proton pump inhibitors leading to acute kidney injury and/or chronic renal failure, 21 April 2021	1.3.1.2
4	Safety issue, SAHPRA communication, Proton Pump Inhibitors (PPIs) - increased risk of subclinical acute or chronic interstitial nephritis associated with PPIs leading to chronic renal inflammation and reduced renal function, 15 December 2020	1.3.1.2
5	Current FDA approved innovator SmPC: Nexium, delayed release capsules, 20 and 40mg, AstraZeneca UK Limited, U.S, Nov 2020	1.3.1.2