PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

PROBITOR 20 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (sucrose 43,350 mg).

3. PHARMACEUTICAL FORM

PROBITOR 20 is a white capsule filled with almost white to light brown pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROBITOR 20 is indicated in:

***Adults*:**

- Treatment of duodenal ulcer, 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 programme with appropriate antibiotics.

- Treatment of non-steroidal anti-inflammatory drugs (NSAIDs)-associated gastric and/or duodenal ulcer 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 (> 20 kg)*:**

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

4.2 Posology and method of administration

PROBITOR 20 is recommended to be given in the morning and swallowed whole with a half glass of liquid. The contents of the PROBITOR 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 patients refractory to other treatment regimens, 40 mg once daily may be effective.

Gastric ulcer and reflux oesophagitis:

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

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. 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 PROBITOR 20 in children (see section 4.4).

Severe ulcerative reflux oesophagitis in children > 20 kg:

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

This formulation is not suitable for children less than < 20 kg.

Elderly:

Dose reductions are not necessary in elderly patients.

Impaired renal function:

Dose reductions are not necessary in renal impairment.

Impaired hepatic function:

Bioavailability and plasma half-life of PROBITOR 20 are increased in patients with impaired hepatic function.

The long-term safety of PROBITOR 20 in patients with renal and hepatic impairment has not been established (see section 4.4).

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.

PROBITOR 20 must not be used concomitantly with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

In the presence of any alarm symptoms (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 PROBITOR 20 may alleviate symptoms and delay diagnosis

Co-administration of atazanavir with PROBITOR 20 is not recommended (see section 4.5).

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

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

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

PROBITOR 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.

PROBITOR 20 is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered.

An interaction is observed between clopidogrel and PROBITOR 20 (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of PROBITOR 20 and clopidogrel should be avoided.

Effects related to acid inhibition:

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

Decreased gastric acidity increases gastric counts of bacteria normally present in the gastro-intestinal tract.

Treatment with PROBITOR 20 may lead to slightly increased risk of gastro-intestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile* (see section 5.1). For patients using PROBITOR 20, a diagnosis of *Clostridium difficile* associated diarrhoea (CDAD) should be considered with diarrhoea that does not improve. Patients should be advised to seek immediate care from a healthcare professional if they experience watery stools, abdominal pain and fever while taking PROBITOR 20. Patients should use the lowest

dose and shortest duration of PROBITOR 20 therapy appropriate to the condition being treated.

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 PROBITOR 20. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, PROBITOR 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 proton pump inhibitor treatment.

Sucrose:

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

PROBITOR 20 contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

For long-term treatment:

PROBITOR 20 may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like PROBITOR 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 PROBITOR 20.

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

PROBITOR 20, 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. PROBITOR 20 may increase the overall risk of fracture by 10 to 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 (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

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). PROBITOR 20 should be discontinued in cases of suspected TIN, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicines and other forms of interaction

Effects of PROBITOR 20 on the pharmacokinetics of other active substances

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with PROBITOR 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 PROBITOR 20.

Concomitant administration of PROBITOR 20 with nelfinavir is contraindicated (see section 4.3).

Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacologically active metabolite M8 was reduced by approximately 75 to 90 %. The interaction may also involve CYP2C19 inhibition.

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

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. 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 PROBITOR 20 and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been reported. Caution should be exercised when PROBITOR 20 is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

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

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

PROBITOR 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 medicinal products are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when PROBITOR 20 is given concomitantly.

Cilostazol

PROBITOR 20, given in doses of 40 mg to healthy patients 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 PROBITOR 20 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 PROBITOR 20 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 dose of tacrolimus adjusted if needed.

Methotrexate

When given together with PROBITOR 20, methotrexate levels, have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of PROBITOR 20 may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since PROBITOR 20 is metabolized by CYP2C19 and CYP3A4 active substances known to inhibit CYP2C19 and 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. PROBITOR 20 increased voriconazole C_{max} and AUC by 15 % and 41 %, respectively. 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.

Plasma concentrations of omeprazole and clarithromycin may be increased during concomitant administration. There is no interaction with metronidazole or amoxicillin.

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 the rate of metabolism of PROBITOR 20.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

PROBITOR 20 may lead to drowsiness and impaired concentration. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or 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 side effects 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).

Blood and the lymphatic system disorders:

Less frequent: Pancytopenia, thrombocytopenia, agranulocytosis and leucopoenia.

Immune system disorders:

Less frequent: Hypersensitivity reactions: hypersensitivity with anaphylaxis and fever, angioedema, bronchospasms and anaphylactic shock.

Endocrine disorders:

***Less frequent*:** Hyponatraemia, hypomagnesaemia and hypocalcaemia.

Nervous system disorders:

Frequent: Headache (severe enough to require discontinuation of therapy in some cases), vertigo, dizziness, somnolence and insomnia.

Less frequent: Paraesthesia, reversible mental confusion, aggression, hallucinations, agitation and depression.

Eye disorders:

Less frequent: Blurred vision

Cardiac disorders:

Less frequent: Peripheral oedema

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 and abdominal pain or colic.

Less frequent: Taste disturbances, benign reversible gastric glandular cysts, dry mouth, stomatitis, oesophageal candidiasis, acid regurgitation and increased gastro-intestinal bacteria.

***Not known*:** Microscopic colitis

Hepatobiliary disorders:

***Frequent*:** Raised liver enzymes.

***Less frequent*:** Hepatitis with or without jaundice and hepatic encephalopathy, hepatic failure.

Skin and subcutaneous tissue disorders:

Less frequent: Photosensitivity, bullous eruption, erythema multiforme, pruritus, dermatitis, urticaria, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome and alopecia.

***Not known*:** Subacute cutaneous lupus erythematosus (see section 4.4)

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Asthenia, arthralgia, myalgia. Fracture of the hip, wrist or spine and muscular weakness.

Renal and urinary disorders:

Less frequent: Tubulointerstitial 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, impotence

General disorders and administration site conditions:

Less frequent: Malaise, fever, increased sweating.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via the link: Sandoz (iqvia.com) or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

There is limited information available on the effects of overdoses of PROBITOR 20 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, headache, blurred vision, diaphoresis, flushing, malaise and tachycardia have been reported. Also apathy, depression and confusion have been described in single cases.

Due to extensive protein binding, omeprazole is not readily dialysable There is no specific antidote for overdose with omeprazole.
Treatment if needed is symptomatic.
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 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 inhibits both basal and stimulated gastric acid secretion by parietal cells, whether induced by acetylcholine, gastrin or histamine.Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.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 ≥ 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* 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.

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 to 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 %. Bioavailability depends on dose and gastric pH, and may reach 70 % with repeated administration.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0,3 l/kg body weight.Omeprazole is 97 % plasma protein bound.

Biotransformation

Clearance from the circulation is by hepatic metabolism, with a plasma half-life of 30 to 90 minutes. Hepatic metabolism occurs primarily via the cytochrome P450 (CYP) isoform (CYP2C19). 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 plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing.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. 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. 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 % are excreted via 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 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine, hypromellose, magnesium oxide heavy, methacrylic acid – ethyl achrylate copolymer 1:1 dispersion, povidone K25, sodium lauryl sulphate, sugar spheres (sucrose), talc and triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original packaging in order to protect from light and moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

PROBITOR 20 is packaged in HDPE plastic bottles with polypropylene or CRC polypropylene screw caps with induction heat seal liner and 1 g silica gel capsules or in aluminium blisters, packed in cardboard cartons in packs of 14, 28, 30, 56 and 60 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

43/11.4.3/0458

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 June 2014

10. DATE OF REVISION OF THE TEXT

14 August 2024

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