SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NOZER 20 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Omeprazole	20 mg

Preservatives:

Methylparaben	0,15 % *m/m*
Propylparaben	0,04 % *m/m*

Contains sugar.

Each NOZER capsule:

Contains sucrose 165,95 mg and lactose anhydrous 2,99 mg.

Contains sweetener mannitol 55,90 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules.

Size 2 hard gelatin capsules with a dark blue body and a light blue cap, containing white to almost white uniformly rounded enteric-coated pellets. “NOZER**”** is printed on both the shells with white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOZER 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 gastroesophageal reflux disease (GERD) 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 a 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

Posology

THE RECOMMENDED DOSAGES FOR ADULTS

Duodenal ulcer

20 mg once daily for two to four weeks.

In some duodenal ulcer patients 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 to 20 – 40 mg once daily.

The above, recommended dosage regimens, are inclusive of *Helicobacter pylori*–positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

Gastric ulcer and reflux oesophagitis

20 mg once daily for four to eight weeks.

In some gastric ulcer and reflux oesophagitis patients 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 – 40 mg once daily.

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with NOZER 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 (GERD)

20 mg daily.

Patients may respond adequately to 10 mg daily, therefore individual dose adjustments should be considered.

If symptom control has not been achieved after 2 weeks of treatment with 20 mg daily, further investigation is recommended.

If gastroesophageal reflux disease (GERD) symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, especially where differentiation of diagnosis of GERD with angina and congestive heart failure is present, 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.

There is very limited experience with the use of NOZER in children (see section 4.4).

THE RECOMMENDED DOSAGES FOR CHILDREN

Severe ulcerative reflux oesophagitis in children from one year and older

Weight:	**Dosage:**
10 – 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 NOZER in patients with renal and hepatic impairment has not been established (see sections 4.8 and 5.2).

Impaired renal function

Dose reductions are not necessary in renal impairment (see sections 4.4 and 5.2).

Impaired hepatic function

Bioavailability and plasma half-life of NOZER are increased in patients with impaired hepatic function, therefore a daily dose of 10 – 20 mg is generally sufficient (see sections 4.4, 4.8 and 5.2).

Paediatric population

There is very limited experience with the use of NOZER in children (see sections 4.4, 4.8 and 5.2).

NOZER should not be used in children under 1 year of age or < 10 kg.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to omeprazole or to any of the excipients listed in section 6.1.
- Known hypersensitivity to substituted benzimidazoles.
- Safety in pregnancy and lactation has not been established (see section 4.6).
- NOZER must not be used concomitantly with nelfinavir (see sections 4.4 and 4.5).
- Co-administration of atazanavir with NOZER is not recommended (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Gastric malignancy

Prior to treatment or in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, or melaena), the possibility of malignancy or gastric ulcer or a malignant disease of the oesophagus should be excluded as the treatment with NOZER may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

***Clostridium difficile*-associated diarrhoea**

Proton pump inhibitor (PPI) therapy like NOZER may be associated with an increased risk of *Clostridium difficile-associated* diarrhoea (CDAD), especially in hospitalised patients.

This diagnosis should be considered for diarrhoea that does not improve (see section 4.8).

Patients should use the lowest dose and shortest duration of NOZER therapy appropriate to the condition being treated.

Acute interstitial nephritis (AIN) leading to acute kidney injury (AKI) and/or chronic kidney disease

NOZER may increase the risk of subclinical acute interstitial nephritis (AIN) associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function (tubular injury being “tubulointerstitial nephritis” also called “Acute interstitial nephritis (AIN)”) (see section 4.8).

AIN has been observed in patients taking PPIs, such as NOZER, and may occur at any point during PPI therapy. AIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium and can progress to acute kidney injury (AKI) (acute renal failure).

AIN may be drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medicine or drug exposure.

Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decrease renal function (e.g., malaise, nausea, anorexia). A delay in diagnosis and continued use of the PPI can lead to chronic renal failure.

Patients on treatment with PPIs must be frequently monitored for renal function and the urine checked for haematuria and/or proteinuria. Patients should be advised to report any

decrease in urine volumes or if they suspect that there is blood in their urine. Treatment with PPIs should be discontinued in patients with AIN.

Concomitant administration with nelfinavir and atazanavir

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Concomitant administration of proton pump inhibitors such as omeprazole as in NOZER with nelfinavir is contraindicated and with atazanavir is not recommended (see sections 4.3 and 4.5).

If the combination of atazanavir with NOZER 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.

Hepatic and renal impairment

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

Hepatic impairment may require a reduction in dose (see sections 4.2 and 5.2).

Interaction with clopidogrel

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medicines, such as NOZER, that interfere with CYP2C19 activity. Avoid concomitant use of clopidogrel and NOZER. Concomitant use of clopidogrel with 80 mg omeprazole, reduced the pharmacological activity of clopidogrel even when administered 12 hours apart. When using NOZER, consider alternative anti-platelet therapy (see section 4.5).

The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of NOZER and clopidogrel should be discouraged.

Bone fractures

Proton pump inhibitors, such as NOZER, 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 (see section 4.8).

Observational studies suggest that proton pump inhibitors 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.

Hypomagnesaemia

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 dysrhythmia 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 such as NOZER with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitor (PPI) therapy like NOZER is associated with very infrequent cases of SCLE (see section 4.8). 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 NOZER. SCLE after previous treatment with NOZER may increase the risk of SCLE with other proton pump inhibitors.

Vitamin B_{12} absorption

NOZER, 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.

Atrophic gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole**.**

Gastrointestinal infections

Decreased gastric acidity increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with NOZER may lead to slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter* (see section 4.8).

Gastric glandular cysts

During long-term treatment gastric glandular cysts have been reported in somewhat increased frequency (see section 4.8). These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Interactions with diagnostic investigations for neuroendocrine tumours

Serum chromogranin A (CgA) levels increase secondary to medicine-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumours.

To avoid this interference, NOZER treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of NOZER treatment.

Concomitant administration with methotrexate

Concomitant use of PPIs such as NOZER with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of NOZER may be considered in some patients (see section 4.5).

Concomitant use with St John's Wort or rifampicin

Medicines which induce CYP2C19 or CYP3A4 (such as St John's Wort or rifampicin) can substantially decrease omeprazole concentrations. Avoid concomitant use of NOZER with St John's Wort or rifampicin.

Prolonged use of NOZER

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

Excipient sucrose

NOZER contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Excipient lactose

NOZER contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Excipient mannitol

NOZER contains mannitol which, on rare occasions, may cause hypersensitivity reactions and may have a laxative effect.

Paediatric population

There is very limited experience with the use of NOZER in children.
Some children with chronic illnesses may require long-term treatment although it is not recommended.

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 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 sections 4.3 and 4.4). 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 to 90 %. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see sections 4.3 and 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) as in NOZER and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % as consequence of the increased intragastic pH.. 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 then be reinforced.

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.

Substances metabolised by CYP2C19

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

Clopidogrel

Clopidogrel is metabolised to its active metabolite in part by CYP2C19. Co-administration of clopidogrel with omeprazole, an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel given concomitantly or 12 hours apart. Concomitant use of medicines that inhibit the activity of this enzyme may result in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in inhibition of platelet aggregation.

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).

Coumarin anticoagulants

The elimination of R-warfarin and other vitamin K antagonists may be prolonged when NOZER is given concomitantly. Monitoring of INR is recommended and dosage reductions may be necessary.

Cilostazol

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

Diazepam

The elimination of diazepam may be prolonged when NOZER is given concomitantly.

Phenytoin

The elimination of phenytoin may be prolonged when NOZER is given concomitantly.

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.

Active substances metabolised by CYP3A4

Tacrolimus

Concomitant administration of omeprazole as in NOZER has been reported to increase the serum levels of tacrolimus due to decreased CYP3A4 metabolism 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.

Unknown mechanism

Saquinavir

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

Methotrexate

When given together with proton-pump inhibitors, such as NOZER 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.

Voriconazole

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.

Clarithromycin

It has been reported that use of omeprazole with clarithromycin in healthy volunteers resulted in an approximate 30 % increase in peak plasma concentrations of omeprazole, and an increase in its mean half-life from 1,2 to 1,6 hours. At the same time, plasma concentrations of clarithromycin were also modestly increased, as were local concentrations in gastric tissue and mucus. Clarithromycin inhibits the metabolism of omeprazole mediated by the cytochrome P450 isoenzyme CYP3A4.

The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

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.

Other interactions

Concomitant administration with medicines that may cause hypomagnesaemia

Proton pump inhibitors including, omeprazole as in NOZER, can cause hypomagnesaemia when used for a prolonged period, and the risk may be further increased when combined with other medicines that also have this effect.

For patients expected to be on prolonged treatment or who take NOZER with medicines that may cause hypomagnesaemia such as digoxin, tacrolimus or diuretics, measuring of

magnesium levels before starting NOZER treatment and periodically during treatment should be considered (see section 4.4).

Alcohol or food

The absorption of NOZER is not affected by alcohol or food.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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

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

NOZER may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Adverse drug reactions such as dizziness, visual disturbances and vertigo may occur (see section 4.8). 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

a) Summary of the safety profile

It is reported that the most common side effects (1 – 10 %) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with omeprazole.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations			*Clostridium difficile*-associated diarrhoea
Blood and lymphatic system disorders		leukopenia, thrombocytopenia, agranulocytosis, pancytopenia	

Immune system disorders		hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock	
Metabolism and nutrition disorders		hyponatraemia	hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia; hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	insomnia	agitation, confusion, depression, aggression, hallucinations	
Nervous system disorders	headache, dizziness, paraesthesia, somnolence	taste disturbance	
Eye disorders		blurred vision	

Ear and labyrinth disorders	vertigo		
Respiratory, thoracic and mediastinal disorders		bronchospasm	
Gastrointestinal disorders	abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)	dry mouth, stomatitis, gastrointestinal candidiasis	microscopic colitis
Hepatobiliary disorders	increased liver enzymes	hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease	

Skin and subcutaneous tissue disorders	dermatitis, pruritus, rash, urticaria	alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)	subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	fracture of the hip, wrist or spine	arthralgia, myalgia, muscular weakness	
Renal and urinary disorders		interstitial nephritis (see section 4.4)	
Reproductive system and breast disorders		gynaecomastia	
General disorders and administration site conditions	malaise, peripheral oedema	increased sweating	

d. Paediatric population

The adverse event profile was generally the same in children as for adults in short- as well as in long-term treatment for acid-related disease. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth. (see sections 4.2, 4.4 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Blurred vision, confusion, diaphoresis, flushing, headache, malaise, nausea, and tachycardia have been reported from over-dosage with omeprazole.

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 medical practitioner / doctor consultation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 11.4.3 Medicines acting on the gastrointestinal tract – Other

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors,

ATC code: A02BC01

Mechanism of action

Omeprazole is a proton pump inhibitor and reduces gastric acid secretion. It is a specific inhibitor of gastric proton pump in the parietal cell.

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

acid secretion and stimulated acid secretion, irrespective of the secretagogue. Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

Pharmacodynamic effects

Effect on gastric secretion

Oral dosing with omeprazole 20 mg once daily provides inhibition of gastric acid and secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80 % in twenty-four hour intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70 %, twenty-four hours after dosing with omeprazole.

5.2 Pharmacokinetic properties

Absorption

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules. Absorption of omeprazole takes place in the small intestine and is usually completed within 3 - 6 hours. The systemic bioavailability of omeprazole from a single oral dose of omeprazole is approximately 35 %. After repeated once daily administration, the bioavailability increases to about 60 %.

Orally administered omeprazole is well absorbed but to a variable extent. Absorption of omeprazole takes place in the small intestine and is usually completed within three to six hours. Concomitant intake of food has no influence on the bioavailability.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0,3 L/kg and a similar value is also seen in patients with renal insufficiency. In elderly and in patients with

hepatic insufficiency, the volume of distribution is slightly decreased. The plasma protein binding of omeprazole is about 95 %.

Biotransformation

Omeprazole is entirely metabolised by the cytochrome P450 (CYP), mainly in the liver. A major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase) to form hydroxy-omeprazole, and to a small extent by CYP3A4 to form omeprazole sulfone. Identified metabolites in plasma are the sulfone, the sulfide and hydroxy-omeprazole, these metabolites are inactive having no significant effect on acid secretion.

Elimination

About 80 % of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxyl-omeprazole and the corresponding carboxylic acid.

Clearance from the plasma is with an elimination half-life of 30 to 90 minutes.

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.

Linearity/non-linearity

The absorption of omeprazole appears to be dose-dependent -increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion resulting in a non-linear dose-AUC relationship after repeated administration. In addition, bioavailability is higher after long-term use.

This time- and dose-dependency is due to a decrease of first pass hepatic metabolism due to saturation and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone).

Hepatic impairment

The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased area under the plasma concentration - time curve (AUC). Omeprazole has not shown any tendency to accumulate with once daily dosing (see section 4.2).

Renal impairment

The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function (see section 4.2).

Elderly

The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75 - 79 years of age) (see section 4.2).

Polymorphism

The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are poor metabolisers of omeprazole. This occurs in about 3 % of

Caucasians and 15 % of Chinese, Japanese, and Koreans. These individuals have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A4. and some by CYP2D6 to form desmethylomeprazole.

Paediatric population

Limited data from children (1 year and older), do not suggest significant differences in the pharmacokinetics of omeprazole within the recommended dosages between children and adults (see sections 4.2, 4.4 and 4.8).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content

Sugar pellets (consisting of sucrose and purified water)

Mannitol

Lactose anhydrous

Purified talc

Sodium lauryl sulfate

Povidone/Polyvinyl pyrrolidone (PVPK-30)

Anhydrous disodium hydrogen phosphate

Sucrose (sugar)

Hypromellose phthalate/Hydroxypropyl methylcellulose phthalate (HPMCP-55)

Cetyl alcohol

Titanium dioxide

Capsule shell

Gelatine

Methylparaben (preservative)

Propylparaben (preservative)

Cap - light blue

Brilliant blue (CI 42090)

Erythrosine (CI 45430)

Quinoline yellow (CI 47005)

Titanium dioxide (CI 77891)

Carmosine (CI 14720)

Body - dark blue

Brilliant blue (CI 42090)

Carmosine (CI 14720)

Erythrosine (CI 45430)

Quinoline yellow (CI 47005)

Titanium dioxide (CI 77891)

White printing ink

Absolute alcohol

Isopropyl alcohol

Shellac dewaxed powder

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light. Keep the aluminium strip packs in the outer carton until required for use.

6.5 Nature and contents of container

6 capsules in aluminium strip pack:

5 of these strips in one carton i.e. 30 capsules pack.

7 capsules in aluminium strip pack:

4 of these strips in one carton i.e. 28 capsules per pack.

10 capsules in aluminium strip pack:

3 of these strips in one carton i.e. 30 capsules per pack.

or 10 of these strips in one carton i.e. 100 capsules per pack.

14 capsules in aluminium strip pack:

1 of these strips in one carton i.e. 14 capsules per pack

or 2 of these strips in one carton i.e. 28 capsules per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd

Loch House Unit 003

3A Eton Road, Parktown

Johannesburg, 2193

8. REGISTRATION NUMBER

36/11.4.3/0420

9. DATE OF FIRST AUTHORISATION

02 July 2004

10. DATE OF REVISION OF THE TEXT

22 August 2021