APPROVED PROFESSIONAL INFORMATION FOR PEPTISEC

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEPTISEC 10 hard gelatine gastro-resistant capsules

PEPTISEC 20 hard gelatine gastro-resistant capsules

PEPTISEC 40 hard gelatine gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PEPTISEC hard gelatine gastro-resistant capsule contains either 10, 20 or 40 mg omeprazole.

PEPTISEC 10 contains sugar (mannitol, 2,5 mg and sucrose, no more than 6,1 mg per capsule).

PEPTISEC 20 contains sugar (mannitol, 5,0 mg and sucrose, no more than 12,3 mg per capsule).

PEPTISEC 40 contains sugar (mannitol, 10,0 mg and sucrose, no more than 24,5 mg per capsule).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PEPTISEC 10**:** Hard gelatine capsule size “4”, with opaque green cap and opaque

white body, containing white to off-white or white cream spherical regular pellets without detectable defects.

PEPTISEC 20**:** Hard gelatine capsule size “4”, with opaque blue cap and opaque white body, containing white to off-white of white cream spherical regular pellets without detectable defects.

PEPTISEC 40**:** Hard gelatine capsule size “3”, with opaque white cap and opaque grey body, containing white to off-white or white cream spherical regular pellets without detectable defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEPTISEC 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 programme with appropriate antibiotics.
- Treatment of non-steroidal anti-inflammatory drugs (NSAID)-associated gastric and/or duodenal ulcer/erosions.
- Reduction of the risk to develop gastric and/or duodenal ulcer/erosions and

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reduction of the risk of relapse for previously healed gastric and/or duodenal ulcer/erosions in patients on NSAID 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

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.

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For the long-term management of patients with reflux oesophagitis the recommended dose is 20 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 PEPTISEC at a dosage of 20 mg once daily.

NSAID-associated gastro-duodenal 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 NSAID-associated gastro-duodenal lesions and dyspeptic symptoms

20 mg once daily.

Symptomatic gastro-oesophageal reflux disease

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.

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Zollinger-Ellison Syndrome

60 mg once daily.

The dosage should be adjusted individually and treatment continued as long as it is 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 PEPTISEC in children (see section 4.4).

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

Recommended dosages:

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.

Impaired renal function:

Dose reductions are not necessary in renal impairment.

Impaired hepatic function:

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

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

Method of administration:

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

4.3 Contraindications

- Hypersensitivity to omeprazole or to any of the other ingredients of PEPTISEC (see section 6.1).
- Safety in pregnancy and lactation has not been established.
- PEPTISEC must not be used concomitantly with nelfinavir.
- Co-administration of atazanavir with PEPTISEC is not recommended

4.4 Special warnings and precautions for use

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

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

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

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

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

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

PEPTISEC, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

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

Increased risk of bone fractures

PEPTISEC, 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 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.

Increased risk of hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like PEPTISEC 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 PEPTISEC with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PEPTISEC treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitor (PPI) therapy like PEPTISEC is 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 PEPTISEC. SCLE after previous treatment with PEPTISEC may increase the risk of SCLE with other proton pump inhibitors.

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Interference with laboratory tests

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

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 PEPTISEC may lead to an increased risk of gastro-intestinal infections such as *Salmonella*, *Campylobacter* or *C. difficile*.

Clostridium-difficile-associated diarrhoea

Proton pump inhibitor (PPI) therapy like PEPTISEC 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 PEPTISEC therapy appropriate to the condition being treated.

Acute Tubulointerstitial Nephritis

Acute Tubulointerstitial Nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. TIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute

interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury. TIN may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to medication exposure. 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 extrarenal manifestations (e.g., fever rash or arthralgia). Discontinue PEPTISEC and evaluate patients with suspected acute TIN.

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

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

Excipient warning

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

PEPTISEC contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

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 platelet inhibition.Omeprazole is metabolised via the hepatic P450 cytochrome enzyme system, which may affect the metabolism of other medications metabolised by these enzymes, when given concomitantly. The elimination of diazepam, warfarin and phenytoin may be prolonged when omeprazole is given concomitantly. Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when omeprazole is given concomitantly. There may be interactions with other medicines, which are also metabolised via the cytochrome P450 enzyme system.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced (see Section 4.4).

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase

or decrease the absorption of activesub stances with a gastric pH dependent absorption.

Nelfinavir and atazanavir

In case of co-administration with omperazole, the plasma levels of nelfinavir and atazanavir are decreased. Concomitant administration of omeprazole with nelfinavir is contraindicated (see Section 4.3). Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40 % and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 to 90 %. The interaction may also involve CYP2C19 inhibition. Concomitant administration of omeprazole with atazanavir is not recommended. 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.

Active substances metabolised by CYP2C19

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

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Cilostazol

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

Phenytoin

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

Saquinavir

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

Tacrolimus

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

Methotrexate

When given together with omeprazole, 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.

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.

Inhibitors CYP2C19 and/or CYP3A4

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

Inducers of CYP2C19 and/or CYP3A4

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

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines:

PEPTISEC may lead to drowsiness and impaired concentration that may be

aggravated by the simultaneous intake of alcohol or other central nervous system depressants. 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 common side effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequency unknown	*Clostridium-difficile*-associated diarrhoea
Blood and lymphatic system disorders	Less frequent	Leucopenia, thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions (e.g. fever, angioedema, anaphylactic reaction/shock)
Endocrine disorders	Less frequent	Gynaecomastia
Metabolism and nutrition disorders	Less frequent Frequency unknown	Hyponatraemia, hypomagnesaemia Severe hypomagnesaemia may result in hypocalcaemia.

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		Hypomagnesaemia may also be associated with hypokalaemia
Psychiatric disorders	Less frequent	Reversible mental confusion, agitation, aggression, depression and hallucinations (predominantly in severely ill patients), insomnia
Nervous system disorders	Frequent Less frequent	Headache (severe enough to cause discontinuation in some patients) Dizziness, somnolence, insomnia, paraesthesia
Eye disorders	Less frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Vertigo
Vascular 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 patients), constipation, abdominal pain or colic, nausea, vomiting, flatulence,

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		gastric glandular cysts, fundic gland polyps (benign)
	Less frequent	Dry mouth, stomatitis, oesophageal candidiasis, taste disturbances
	Frequency unknown	Microscopic colitis
Hepato-biliary disorders	Less frequent	Raised liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy (in patients with pre-existing liver disease), hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Skin rash, urticaria, pruritus, photosensitivity, bullous eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, alopecia, erythema multiforme, toxic epidermal necrolysis (TEN), dermatitis acute generalised exanthematous pustulosis (AGEP) drug reaction with eosinophilia and systemic symptoms (DRESS)
	Frequency unknown	Subacute cutaneous lupus erythematosus (see section 4.4)

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Musculoskeletal, and connective tissue disorders	Less frequent	Asthenia, arthralgia, myalgia, bone fracture (fracture of the hip, wrist or spine), muscular weakness
Renal and urinary disorders	Less frequent	Tubulointerstitial nephritis (wth possible progression to renal failure)
General disorders and administration site conditions	Less frequent	Malaise, increased sweating

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “Adverse drug reaction and quality problem reporting form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

4.9 Overdose

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

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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

11.4.3 Medicines acting on the gastrointestinal tract – Other

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

Omeprazole is an inhibitor of the gastric proton pump (H+, K+-ATPase). 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.

5.2 Pharmacokinetic properties:

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. Bioavailability depends on dose and gastric pH and may reach 70 % with repeated administration. Food has no influence on the bioavailability of omeprazole. Omeprazole is more than 95 % bound to plasma proteins. 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). The inactive metabolites are excreted mainly in the urine (80 %) whilst the remaining 20 % are excreted via the faeces. 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.

5.3 Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H_2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Anhydrous disodium phosphate

Hypromellose Type 2910

Macrogol 6000

Magnesium hydroxide

Mannitol

Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)

Polysorbate 80

Purified Water

Sodium Lauryl sulfate

Sodium Starch Glycolate (Type A)

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Sugar Spheres (containing sucrose and maize starch)

Talc

Titanium Dioxide

Hard gelatine capsule shell:

PEPTISEC 10**:** The capsule shell contains Brilliant blue FCF - FD&C Blue 1 (E133), gelatine, titanium dioxide (E171) and yellow iron oxide.

PEPTISEC 20**:** The capsule shell contains Indigotine-FD&C Blue 2 (E132), gelatine and titanium dioxide (E171).

PEPTISEC 40: The capsule shell contains black iron oxide, gelatine and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original package in order to protect from moisture.

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

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Transparent PVC-PE-PVDC/Aluminium blisters.

White HDPE bottles with silica gel desiccant contained in the cap.

Pack size: 7, 14, 28, 30, 56 or 100 hard gelatine gastro-resistant capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBERS

PEPTISEC 10: 56/11.4.3/0835

PEPTISEC 20: 56/11.4.3/0836

PEPTISEC 40: 56/11.4.3/0837

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 10 October 2023