PROFESSIONAL INFORMATION FOR HEPRALOC 40 IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

HEPRALOC 40 IV (40 mg powder for solution for injection).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 40 mg pantoprazole as pantoprazole sodium sesquihydrate.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white Lyophilized cake or powder. When constituted as directed the solution should be colorless to light yellow color, clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

HEPRALOC 40 IV is indicated for intravenous administration in patients who cannot be treated orally

HEPRALOC 40 IV is indicated for:

- The short-term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis.
- If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infections, **HEPRALOC 40 IV** used in combination with appropriate antibiotics may be useful.
- The treatment of Zollinger-Ellison Syndrome

4.2. Posology and method of administration

Posology:

The recommended dose is one vial (40 mg) of **HEPRALOC 40 IV** per day.

HEPRALOC 40 IV is indicated for intravenous administration in patients who cannot be treated orally.

A ready-to-use solution is prepared by injecting 10 ml of a 0,9 % sodium chloride solution into the vial containing the freeze-dried powder. The solution may be administered directly or may be diluted further by mixing with 100 ml 0,9 % sodium chloride or 5 % glucose ONLY.

The product should be administered intravenously over 2 to 15 minutes.
After preparing the solution in 0,9 % sodium chloride and 5 % dextrose the solution must be used immediately and any unused portion discarded.

HEPRALOC 40 IV may be used intravenously for up to 7 days. As soon as oral therapy is possible, treatment should be replaced with the same oral dose (of a suitable oral formulation of pantoprazole) in compliance with the approved dosage regimen as stated below.

Duodenal ulcer:

The recommended dose is 40 mg pantoprazole daily. The total treatment with intravenous and oral pantoprazole should be 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **HEPRALOC 40 IV** or an oral pantoprazole formulation used in combination with appropriate antibiotics may be useful.

Gastric ulcer:

The recommended dose is 40 mg pantoprazole once daily. In the case of a suspected gastric ulcer, malignancy of the gastric ulcer should be excluded, as treatment could conceal the symptoms and may delay the diagnosis.

Reflux oesophagitis:

The recommended dose is 40 mg pantoprazole once daily.

Zollinger-Ellison syndrome:

For management of Zollinger-Ellison syndrome, the patient should start treatment with a daily dosage of 80 mg (2 vials) of **HEPRALOC 40 IV**. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses above 80 mg, the dosage should be divided and given twice daily.

In case rapid acid control is required, a starting dose of 2 x 80 mg **HEPRALOC 40 IV** is sufficient to manage a decrease of acid output into the target range (< 10 mmol/h) within one hour in the majority of patients. Transition from **HEPRALOC 40 IV** to an oral formulation should be performed as soon as it is clinically justified.

Long-term treatment:

Long-term treatment with **HEPRALOC 40 IV** is currently not indicated as there is insufficient clinical data.

Elderly patients:

No dosage adjustment is needed in the elderly.

Impaired renal and liver function:

No dosage adjustment is required in impaired renal function.

A daily dose of 20 mg pantoprazole should not be exceeded in patients with mild to moderate severe liver impairment (see sections 4.4 and 5.2).

Paediatric population

Safety and efficacy in children have not been established (see section 4.3).

Method of administration

For intravenous administration.

4.3. Contraindications

HEPRALOC 40 IV is contraindicated in:

- Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients listed in section 6.1.
- Safety and efficacy in children have not been established.
- Severe impaired liver function (see sections 4.2 and 4.4)
- Co-administration with atazanavir and nelfinavir (see section 4.5).

4.4. Special warnings and precautions for use

HEPRALOC 40 IV is for intravenous route only and must not be administered by any other route.

HEPRALOC 40 IV is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Further investigation is to be considered if symptoms persist despite adequate treatment.

The daily dose of 40 mg **HEPRALOC 40 IV** should not be exceeded in elderly patients or in those with impaired renal function.

Clostridium difficile-associated diarrhoea (CDAD)

Published observational studies suggest that proton pump inhibitor (PPI) therapy, like **HEPRALOC 40 IV**, may be associated with an increased risk of Clostridium difficile-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see section 4.8).

Gastrointestinal infections caused by other bacteria: **HEPRALOC 40 IV** may be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole 40 mg, as in **HEPRALOC 40 IV**, may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Hepatic impairment:

In patients with severe liver impairment, liver enzymes should be monitored regularly during treatment with **HEPRALOC 40 IV**, particularly during long-term use. In the case of a rise in the liver enzymes, **HEPRALOC 40 IV** should be discontinued.

Gastric malignancy:

Symptomatic response to pantoprazole, as in **HEPRALOC 40 IV**, may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded. Further investigation is to be considered if symptoms persist despite adequate treatment.

Daily treatment with acid-blocking medicines including **HEPRALOC 40 IV** over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed.

Co-administration with HIV protease inhibitors:

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir or nelfinavir, due to significant reduction in their bioavailability (see sections 4.3 and 4.5).

Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with PPIs such as **HEPRALOC 40 IV** 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 **HEPRALOC 40 IV** with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), medical practitioners should consider measuring magnesium levels before starting **HEPRALOC 40 IV** treatment and periodically during treatment.

Bone fractures:

PPI's, such as **HEPRALOC 40 IV**, 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 PPI's may increase the overall risk of fracture by 10-40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE):

PPI's, such as **HEPRALOC 40 IV**, are associated with 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 medical practitioner should consider stopping **HEPRALOC 40 IV**. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPI's.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, **HEPRALOC 40 IV** 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 PPI treatment.

Increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function:

There is an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPI's) leading to chronic renal inflammation and reduced renal function. The preferred term to describe the histological findings of tubular injury being "tubulointerstitial nephritis".

Acute tubulointerstitial nephritis 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. Tubulointerstitial nephritis may be medicine-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or medicine exposure.

The risk of tubulointerstitial nephritis leading to chronic inflammation and reduced renal function associated with the use of proton pump inhibitors such as omeprazole, is a class effect.

Excipients:

This medicine contains less than 1 mmol sodium (23 mg)

per 10 ml vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

pH-dependent medication:

HEPRALOC 40 IV may reduce or increase the absorption of medicines whose bioavailability is pH-dependent, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV medicines:

It has been shown that co-administration of atazanavir/ritonavir with omeprazole or atazanavir with lansoprazole resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH-dependent. Therefore, **HEPRALOC 40 IV** must not be co-administered with atazanavir (see section 4.4.).

Cytochrome P450 enzyme system:

The active ingredient of **HEPRALOC 40 IV** is metabolised in the liver via the cytochrome P450 enzyme system. An interaction with other medicines or compounds which are metabolised using the same system cannot be excluded.

No clinical significant interactions were however observed in specific tests with a number of such medicines or compounds, namely antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

Anticoagulants:

The response to anticoagulants such as warfarin, phenprocoumon and acenocoumarol may be affected by concomitant medicines. It is therefore recommended to monitor the patient with additional PT (prothrombin)/INR (International normalised ratio) determinations when **HEPRALOC 40 IV** is initiated, discontinued or given irregularly.

Other antacids:

There were no interactions with concomitantly administered antacids.

Methotrexate:

Concomitant use of PPIs, including **HEPRALOC 40 IV** with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite

hydroxymethotrexate, possibly leading to methotrexate toxicities. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Antibiotics:

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Medicines that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole, as in **HEPRALOC 40 IV**. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment. Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolised through these enzyme systems.

4.6. Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy:

Animal studies have shown reproductive toxicity. Data on pregnant women (between 300 to 1 000 pregnancy outcomes) indicate no malformative or foetal/ neonatal toxicity.

As a precautionary measure, the use of **HEPRALOC 40 IV** should be avoided during pregnancy.

Breastfeeding:

Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded.

Fertility:

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies.

4.7. Effects on ability to drive and use machines

HEPRALOC 40 IV will be administered in a hospital setting. **HEPRALOC 40 IV** has moderate influence on the ability to drive and use machines. Since adverse reactions such as blurred vision and dizziness have been reported in patients receiving **HEPRALOC 40 IV**, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **HEPRALOC 40 IV** does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

Summary of the safety profile:

Side effects are tabulated below into Frequent, less frequent and frequency unknown.

Tabulated summary of adverse reactions:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Gastrointestinal infection	*Clostridium difficile* associated diarrhoea (CDAD)	---
Blood and the lymphatic system	---	Leukopenia, thrombo-cytopenia,	---

disorders		agranulocytosis , pancytopenia	
Immune system disorders	---	Anaphylactic reactions including anaphylactic shock	---
Metabolism and nutrition disorders	---	Elevated triglycerides, elevated cholesterol, Hyper-lipidaemias, weight changes	Hypo-natraemia, hypo-magnesaemia, hypo-kalaemia, Hypocalcaemia .
Psychiatric disorders	---	Mental depression, sleep disorders, disorientation	Hallucination
Nervous system disorders	Headache	Dizziness, taste disorders	Paraesthesia
Eye disorders	---	Disturbances in vision or blurred vision	Anterior ischaemic optic neuropathy
Gastrointestinal disorders	Abdominal pain and discomfort, diarrhoea, constipation or flatulence, fundic gland polyps (benign)	Nausea, vomiting, dry mouth	Gastric glandular cysts, microscopic colitis
Hepatobiliary disorders	---	Increased liver enzymes (transaminases, y-GT), severe hepatocellular damage leading to jaundice with or without hepatic failure increased bilirubin	---
Skin and subcutaneous tissue disorders	---	Allergic reactions such as pruritus and skin rash, urticaria,	Subacute cutaneous lupus erythematosus

		angioedema, severe skin reactions such as Stevens Johnson syndrome, erythema multiforme, Lyell syndrome, photosensitivity, exanthema, eruption	
Musculoskeletal and connective tissue disorders	---	Arthralgia, myalgia, fracture of the hip, wrist or spine	Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders	---	Interstitial nephritis (may lead to renal failure)	---
Reproductive system and breast disorders	---	Gynaecomastia	---
General disorders and administrative site conditions	Injection site thrombo-phlebitis	Peripheral oedema, asthenia, fatigue, malaise, increased body temperature	---

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. Health care providers are asked to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website, and to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9. Overdose

There are no known symptoms of overdosage in man.

Treatment

No specific therapeutic recommendation can be made in cases of overdosage. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 11.4.3 – Medicines acting on the gastrointestinal tract – Other.

Pharmacotherapeutic group: Drugs for acid related disorders, Proton pump inhibitors,

ATC

ATC code: A02BC02

Mechanism of action:

Pantoprazole is a proton pump inhibitor (PPI), i.e. it inhibits specifically and dose-proportionally H+, K+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

Pantoprazole is a substituted benzimidazole, which accumulates in the acidic compartment of the parietal cells after absorption. In the parietal cell it is protonated and chemically re-arranged to the active inhibitor, a cyclic sulphenamide, which binds to the H+, K+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single and multiple intravenous dosing. Because pantoprazole acts distal to receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts it full effect in a strongly acidic environment (pH < 3) and remains

most inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach. Complete pharmacological and therapeutic effect for pantoprazole can therefore only be achieved in the acid-secreting parietal cells. This effect is diminished at the same rate as acid secretion is inhibited, by means of a feedback mechanism.

Effect on gastric secretion:

Following intravenous administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. With 30 mg pantoprazole intravenous, the mean acid inhibition after 5 days was 99 %. The basal 24 hour acidity was reduced by 98 %.

Pantoprazole maintains the physiological pH-rhythm. The values, however, are shifted to higher levels. During the night, periods of pH values approximating placebo have been found to occur.

Although pantoprazole has a half-life of approximately 1 hour, the antisecretory effect increases during repeated administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2. Pharmacokinetic properties

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasmakinetics of pantoprazole are linear after both oral and intravenous administration.

Absorption & Distribution:

Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg. Following intravenous administration of pantoprazole, serum/plasma concentrations decline exponentially. The terminal half-life is about 1 hour. The total serum clearance is approximately 0,1 L/h/kg and the volume of distribution is about 1,5 L/kg.

The plasma kinetics for pantoprazole after both oral and intravenous administration is

linear over the dose range of 10 to 80 mg.

Biotransformation:

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4.

Elimination:

Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole. The balance is excreted in the faeces. The half-life of the main metabolite is approximately 1½ hours, which is slightly longer than that of pantoprazole.

Characteristics in specific groups of subjects or patients:

Special populations:

Poor metabolisers:

Population groups that lack a functional CYP2C19 enzyme are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Hepatic and renal impairment:

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC increases by a factor of 5 to 8, while the maximum serum concentration only increases by a factor of 1,5 in comparison with

healthy subjects.

In patients with renal impairment the half-life of the main metabolite is moderately increased but there is no accumulation at therapeutic doses. The half-life of pantoprazole in patients with renal impairment is comparable to the half-life of pantoprazole in healthy subjects. Pantoprazole is poorly dialysed.

A slight increase in AUC and Cmax occurs in elderly volunteers compared with younger people.

Elderly:

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Paediatric population:

Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

5.3. Preclinical safety data

No information available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Disodium Edetate,

Sodium Hydroxide &,

Water for Injection.

6.2. Incompatibilities

N/A

6.3. Shelf life

24 months

6.4. Special precautions for storage

- Store at or below 25°C
- Keep the vial in the outer carton until required for use.
- Protect the content from light.

KEEP OUT OF SIGHT AND REACH OF CHILDREN.

6.5. Nature and contents of container

10 R 10 ml clear blow back tubular glass vial, USP Type-I with 20 mm Neck.

Pack style: 1 X 10 ml, 5 X 10 ml, and 10 X 10 ml

6.6. Special precautions for disposal <and other handling>

Appropriately dispose any unused or remaining solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No. 2, First floor

74 Waterfall Drive

Midrand

2066

8. REGISTRATION NUMBER(S)

56/11.4.3/0881

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 December 2024

10. DATE OF REVISION OF THE TEXT

14 August 2025