1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

ULCEVAN 20 mg delayed release, enteric coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

Contains sugar: Mannitol 53,08 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated tablets.

ULCEVAN is a coated (light yellow), elliptical, normal biconvex tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ULCEVAN is indicated for the temporary short term relief of heartburn and hyperacidity.

4.2. Posology and method of administration

Posology

Adults

ULCEVAN is indicated for short term relief of heartburn and hyperacidity.

The maximum dose is 20 mg per day and the treatment is for a maximum period of 14 days.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient must be advised to consult a doctor.

Special populations

Elderly population

No dosage adjustment is necessary in the elderly.

Impaired renal and liver function

No dosage adjustment is required in the presence of impaired renal function (mild to moderate).

A daily dose of one ULCEVAN tablet should not be exceeded in patients with mild to moderately severe liver impairment (See Sections 4.4 and 5.2).

Method of administration

For oral administration.

ULCEVAN should be swallowed whole with a little water either before or during breakfast.

4.3. Contraindications

ULCEVAN is contraindicated in:

- Patients with hypersensitivity to pantoprazole or to any excipients in ULCEVAN (see section 6.1).
- Safety in pregnancy and lactation (see section 4.6).
- Safety and efficacy in children have not been established.
- Severely impaired liver function (see sections 4.2 and 4.4)
- Co-administration with atazanavir and nelfinavir and other HIV medicines with pH dependent absorption (See Section 4.5).

4.4. Special warnings and precautions for use

Patients should be advised to consult a medical practitioner if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting with blood, previously had gastric ulcer or gastrointestinal surgery. In these cases, malignancy must be excluded as treatment with ULCEVAN may alleviate symptoms and delay diagnosis.
- They have been taking an indigestion or heartburn remedy continuously for 4 or more weeks in order to control their symptoms.
- They have jaundice or hepatic impairment.

Clostridium difficile associated diarrhoea (CDAD)

Treatment with proton pump inhibitors (PPIs), such as ULCEVAN, have been associated with an increased risk of CDAD, especially in hospitalised patients. If a patient develops persistent diarrhoea, this diagnosis should be excluded. Patients should use the lowest dose and shortest duration of ULCEVAN treatment appropriate to the condition being treated. Treatment with ULCEVAN may lead to slightly increased risk of gastrointestinal infections caused by bacteria (*Salmonella* and *Campylobacter*).

Bone fractures

ULCEVAN, 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. ULCEVAN 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.

Gastrointestinal infections caused by bacteria

ULCEVAN, as a proton pump inhibitor (PPI), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract and may therefore lead to an increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

Mild gastrointestinal complaints

ULCEVAN is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

In the presence of alarm symptoms (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.

Prior to treatment, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with ULCEVAN may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with Proton pump inhibitors (PPIs) like ULCEVAN 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. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors, such as ULCEVAN, 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 healthcare provider should consider stopping ULCEVAN. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Liver impairment

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

Effect on cyanocobalamin (vitamin B12) absorption

Daily treatment with any acid-blocking medicines such as ULCEVAN, over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption or if deficiency symptoms are observed.

Interference with laboratory tests

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

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 drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication 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). In reported case series, some patients were diagnosed on biopsy and in the absence of extrarenal manifestations (e.g. fever rash or arthralgia). Discontinue ULCEVAN and evaluate patients with suspected acute TIN.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Concomitant intake of food has no influence on bioavailability.

ULCEVAN may increase the availability of digoxin if administered for prolonged periods.

Decreased absorption of medicines that are gastric pH dependent

The bioavailability of the following medicines may be reduced when co-administered with ULCEVAN, thereby impacting on their efficacy e.g.

- some azole antifungals such as ketoconazole, itraconazole and posaconazole,
- other medicines such as erlotinib, atazanavir, nelfinavir and other HIV medicines with pH-dependent absorption (see section 4.3)

Coumarin anticoagulants (e.g. warfarin or phenprocoumon)

There have been reports of increased PT (Prothrombin Time)/INR (International Normalised Ratio) in patients receiving proton pump inhibitors, including ULCEVAN.

Therefore, patients must be advised that additional PT/INR determinations may be required when taking ULCEVAN.

Other interactions studies

Pantoprazole, as in ULCEVAN, is extensively metabolised in the liver via the cytochrome P450 enzyme system (by CYP2C19 and other metabolic pathways including oxidation by CYP3A4) and may affect or be affected by other medicines, such as tacrolimis and fluvoxamine, metabolised by the same enzymes. Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs, as in ULCEVAN, that are metabolised through these enzyme systems.

Voriconazole

Voriconazole inhibits the metabolism of proton-pump inhibitors: The exposure of both medicines is increased when ULCEVAN is co-administered with voriconazole.

Methotrexate

Concomitant use of high doses of methotrexate (e.g. 300 mg daily) and ULCEVAN is not recommended as proton-pump inhibitors have been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of ULCEVAN may need to be considered.

There were no interactions with concomitantly administered antacids, and with antibiotics (clarithromycin, metronidazole, amoxicillin).

The elimination of diazepam and phenytoin may be prolonged.

4.6. Fertility, pregnancy and lactation

The safety of ULCEVAN in pregnancy and lactation has not been established. (see section 4.3)

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of ULCEVAN.

Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of ULCEVAN during pregnancy.

Breastfeeding

Animal studies have shown excretion of pantoprazole, as in ULCEVAN, 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. Therefore, a decision should be taken by the medical practitioner on whether to discontinue breast-feeding or to discontinue/abstain from ULCEVAN therapy.

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

ULCEVAN has moderate influence on the ability to drive or operate machinery.

ULCEVAN can cause dizziness and blurred vision.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking ULCEVAN.

4.8. Undesirable effects

a) Summary of the safety profile

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs).

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations			*Clostridium difficile*-associated diarrhoea and increased risk of gastrointestinal infections caused by Salmonella and Campylobacter

Blood and the lymphatic system disorders		Agranulocytosis, leukopenia, thrombocytopenia, pancytopenia	
Immune system disorders		Hypersensitivity (incl. anaphylactic reactions and anaphylactic shock, allergic reactions such as pruritus, skin rash, urticaria and angioedema)	
Metabolism and nutrition disorders		Hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes	Hyponatraemia, hypomagnesaemia, hypocalcaemia[1], hypokalaemia[1]
Nervous system disorders	Headache	Dizziness	Paraesthesia
Eye Disorders		Vision disturbances (blurred vision)	
Psychiatric disorders		Sleep disorders, mental depression, disorientation/confusion	Hallucination
Vascular disorders		Peripheral oedema	
Gastrointestinal disorders	Gastrointestinal complaints such as upper abdominal pain and discomfort, diarrrhoea,constipation,abdominal distention and bloating.	Nausea, vomiting, dry mouth, taste disorders	
Hepato-biliary 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		Severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (TEN) (Lyell syndrome) and photosensitivity, subacute cutaneous lupus erythematosus	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, increased risk of hip, wrist and spine	

		fractures, muscle spasm	
Renal and urinary disorders		Interstitial nephritis	
Reproductive system and breast disorders			Gynaecomastia
General disorders and administrative site conditions		Asthenia, fatigue, malaise, increased body temperature,	

1. Hypocalcemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. 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.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

There are no known symptoms of overdose in man. No specific therapeutic recommendations can be made in the case of an overdose.

Treatment

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 11.4.3 Medicines acting on the gastro-intestinal tract- other.

Pharmacotherapeutic group: Proton pump inhibitors

ATC code: A02BC02

Mechanism of action

Pantoprazole is a proton pump inhibitor, 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 sulphonamide, 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 and oral pantoprazole dosing. Since pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts its full effect in a strongly acidic environment (pH<3) and remains mostly inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach. Therefore, the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

Following oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. The mean acid inhibition was 85 %, 2,5 to 3,5 hours after dosing with pantoprazole 40 mg/day for 7 days. After stopping the administration of pantoprazole, there is no evidence of rebound hypersecretion and 7 days after administering the last dose the acid output is normal.

Pantoprazole maintains the physiological pH rhythm. The values, however, are shifted to higher levels. During the night, periods with 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 once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2. Pharmacokinetic properties

Absorption

Pantoprazole is unstable in acid and is administered orally in the form of an enteric-coated delayed release tablet. Absorption takes place in the small intestine. On average, the maximum plasma concentrations are approximately 2 to 3 µg/mL about 2,5 hours after administration of 40 mg pantoprazole daily, as a single or multiple dose in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

The plasma kinetics of pantoprazole, after oral administration, is linear over the dose range 10 to 80 mg.

Metabolism

Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways 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 with the faeces. The half-life of the main metabolite is approximately 1,5 hours which is slightly longer than that of pantoprazole.

Pharmacokinetic profile in patients with impaired liver or renal function

Hepatic impairment

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC values increase 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.

Renal impairment

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 C_{max} occurs in elderly volunteers compared with younger people.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Basic butylated methacrylate copolymer, calcium stearate, mannitol, sodium carbonate anhydrous, sodium starch glycolate.

Coating:

Hypromellose (E464), kollicoat MAE 30 DP yellow, macrogol, methacrylic acid-ethyl acrylate copolymer dispersion, propylene glycol, sodium lauryl sulfate, talc, titanium dioxide (E171), yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months.

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

Alu/Alu blisters containing 7 tablets per blister strip. 1 or 2 such strips are packed into a carton in pack sizes of 7 or 14 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

48/11.4.3/0763

9. DATE OF FIRST AUTHORISATION

28 February 2022

10. DATE OF REVISION OF TEXT

12 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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