PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PRONIZOR 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRONIZOR 30 mg

Each delayed release capsule contains Lansoprazole 30 mg.

Contains sugar (165,0mg of sucrose).

Excipients:

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Delayed release capsules

PRONIZOR 30 mg

Opaque pink cap/ Opaque black body Size “1” capsule containing white-off white to dark brown delayed release pellets with ‘C85’ on cap and ‘30 mg’ on body imprinted with white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **PRONIZOR 30 mg** is indicated for the short-term treatment of active duodenal ulcers and reflux oesophagitis.
- **PRONIZOR 30 mg** is indicated for Helicobacter pylori-positive duodenal ulcers in conjunction with appropriate antibiotics as part of an eradication program.
- **PRONIZOR 30 mg** is indicated for the short-term treatment of gastric ulcer.

4.2 Posology and method of administration

Posology

One 30 mg capsule once a day for up to eight weeks.

Duodenal ulcer:

The recommended dosage is one 30 mg capsule once a day for 2 to 4 weeks. Patients may respond adequately to 15 mg daily for 2 to 4 weeks, and therefore individual dose adjustments should be considered.

PRONIZOR 30 mg is indicated for *Helicobacter pylori*-positive duodenal ulcers as part of an eradication program, with appropriate antibiotics.

Oesophagitis due to gastro-oesophageal reflux:

The recommended dosage is one 30 mg capsule once a day for 4 weeks. Depending on the endoscopic results, a repeat course of 4 weeks may be necessary. Patients may respond adequately to 15 mg daily for 4 weeks with a second 4 week treatment period, at the same dosage, depending on endoscopic results.

Functional dyspepsia:

Adults: 15 to 30 mg once a day for 2 to 4 weeks.

Elderly:

No dose adjustment is necessary. However, 30 mg per day is the maximum daily dose.

Renal impairment:

No dose adjustment is necessary in renal failure - this also applies to patients on dialysis.

Paediatric patients

Safety and efficacy in children has not been established (see section 4.4).

Method of administration

PRONIZOR 30 mg should preferably be taken before a meal.

4.3 Contraindications

PRONIZOR is contraindicated in**:**

- Patients with hypersensitivity to lansoprazole or to any of the other ingredients contained in **PRONIZOR 30 mg** (see Section 6.1),
- Pregnancy and lactation (see Section 4.6).
- Liver impairment.
- **PRONIZOR 30 mg** should not be used concomitantly with atazanavir and nelfinavir (see Section 4.5).

4.4 Special warnings and precautions for use

Children

Safety and efficacy in children has not been established.

Occurrence of acute interstitial nephritis:

Acute interstitial nephritis has been observed in patients taking PPIs including **PRONIZOR 30 mg** Acute interstitial nephritis may occur at any point during therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue **PRONIZOR 30 mg** if acute interstitial nephritis develops (see section 4.3).

Malignant disease

Treatment with **PRONIZOR 30 mg** may alleviate the symptoms of malignant ulcers and can delay diagnosis. Therefore, the possibility of malignancy of a gastric ulcer or a malignant disease of the oesophagus should be excluded prior to treatment with **PRONIZOR 30 mg**

Malabsorption

Proton pump inhibitors such as **PRONIZOR 30 mg** have been reported to result in a substantial reduction in cyanocobalamin (VitaminB12) absorption, probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy. Proton pump inhibitors such as **PRONIZOR 30 mg** have also been reported to impair the bioavailability of dietary vitamin C. Fat malabsorption, secondary to increased

deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with proton pump inhibitors such as **PRONIZOR 30 mg** treatment. It has been suggested that proton pump inhibitors such as **PRONIZOR 30 mg** can cause calcium malabsorption.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors such as **PRONIZOR 30 mg** are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping **PRONIZOR 30 mg** SCLE after previous treatment with a proton pump inhibitor such as **PRONIZOR 30 mg** may increase the risk of SCLE with other proton pump inhibitors.

Alcohol and CNS depressants

PRONIZOR 30 mg may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.

Hypomagnesaemia

Severe hypomagnesaemia has been reported with the use of PPIs like lansoprazole, as contained in **PRONIZOR 30 mg** 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. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). Other serious events include tremors, carpo-pedal spasm, atrial fibrillation, supraventricular tachycardia, and abnormal QT interval. 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 **PRONIZOR 30 mg** with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting **PRONIZOR 30 mg** treatment and periodically during treatment.

Bone fracture

PPIs like lansoprazole, as contained in **PRONIZOR 30 mg**, especially if used in high doses and over long periods (over 1 year), may increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Reports suggest that PPIs 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.

***Clostridium difficile* associated diarrhoea(CDAD)**

PPIs like lansoprazole, as contained in **PRONIZOR 30 mg** has been linked to an increased risk of enteric infections such as CDAD. A diagnosis of CDAD should be considered for patients taking **PRONIZOR 30 mg** who develop diarrhoea that does not improve.

Symptoms include watery stool, abdominal pain, and fever, and patients may go on to develop more serious intestinal conditions. Factors that may predispose an individual to developing CDAD include advanced age, certain chronic medical conditions, and taking broad spectrum antibiotics. Treatment for CDAD includes the replacement of fluids and electrolytes and the use of special antibiotics.

Reflux Oesophagitis gastric glandular cysts

Diagnosis of reflux esophagitis should be confirmed by endoscopy

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.

Gastrointestinal infections caused by bacteria

Decreased gastric acidity increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with **PRONIZOR 30 mg** may lead to an increased risk of

gastrointestinal infections such as *Salmonella, Campylobacter, Shigella* or *Clostridium difficile*.

Presence of alarm symptoms

In the presence of symptoms such as, significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena, and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with **PRONIZOR 30 mg** may alleviate symptoms and delay diagnosis.

H. pylori

In patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as an etiological factor should be considered.

Long term use

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment should be regularly performed in these patients.

Colitis

Colitis has occurred in patients taking lansoprazole as contained in **PRONIZOR 30 mg** Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.

Excipients

Contains sucrose.

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take **PRONIZOR 30 mg**

4.5 Interaction with other medicines and other forms of interaction

Effects of PRONIZOR 30 mg on other medications

Medicines with pH dependent absorption

PRONIZOR 30 mg may interfere with the absorption of medicines where gastric pH is critical to bioavailability (e.g. ampicillin esters, iron salts).

HIV medications

PRONIZOR 30 mg should not be used with atazanavir or nelfinavir, as it substantially reduces exposure to the HIV-protease inhibitor (see Section 4.3).

Ketoconazole and itraconazole

The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of **PRONIZOR 30 mg** may result in subtherapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

Digoxin

Co-administration of **PRONIZOR 30 mg** and digoxin may lead to increased digoxin plasma levels. The plasma levels of digoxin should therefore be monitored and the dose of digoxin adjusted if necessary when initiating and ending **PRONIZOR 30 mg** treatment.

Medicines metabolised by P450 enzymes

PRONIZOR 30 mg CAPSULES may increase plasma concentrations of medicines that are metabolised by CYP3A4. Caution is advised when combining **PRONIZOR 30 mg** with medicines which are metabolised by this enzyme and have a narrow therapeutic window.

Theophylline

An increase in clearance of theophylline may be seen if given concomitantly with **PRONIZOR 30 mg** Patients may require additional titration of their theophylline dosage when **PRONIZOR 30 mg** is started or stopped to ensure clinically effective blood levels.

Tacrolimus

Co-administration of **PRONIZOR 30 mg** increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with **PRONIZOR 30 mg** is initiated or ended.

Medicines transported by P-glycoprotein

Lansoprazole has been observed to inhibit the transport protein, P-glycoprotein (P-gp) in vitro. The clinical relevance of this is unknown.

Effects of other medicines on PRONIZOR 30 mg

Medicines which inhibit CYP2C19

Fluvoxamine

A dose reduction may be considered when combining **PRONIZOR 30 mg** with the CYP2C19 inhibitor fluvoxamine.

Medicines which induces CYP2C19 and CYP3A4

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin, and St John´s wort (*Hypericum perforatum*) can markedly reduce the plasma concentrations of lansoprazole in **PRONIZOR 30 mg**

Others

Warfarin

Monitoring of patients receiving concomitant warfarin is recommended. Increased INR and prothrombin time in patients receiving **PRONIZOR 30 mg** and warfarin concomitantly have been reported. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Sucralfate / Antacids

The bioavailability and absorption of **PRONIZOR 30 mg** may be decreased with concomitant administration of Sucralfate / antacids. **PRONIZOR 30 mg** should be taken at least 1 hour after taking these medications.

Methotrexate

Lansoprazole as contained in **PRONIZOR 30 mg** has been reported not to affect the pharmacokinetics of methotrexate.

4.6 Fertility, pregnancy and lactation

PRONIZOR 30 mg in contraindicated in pregnancy and lactation (see Section 4.3).

Pregnancy

Adequate and well-controlled studies in humans have not been done.

Lactation

It is not known whether lansoprazole is distributed into breast milk. However, lansoprazole or its metabolites are distributed into the milk of rats. Because lansoprazole has been shown to cause tumorigenic effects in animals, a decision should be made as to whether breastfeeding should be discontinued or the medication withdrawn, taking into account the importance of **PRONIZOR 30 mg** to the mother.

4.7 Effects on ability to drive and use machines

PRONIZOR may lead to drowsiness and impaired concentration. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Summary of the safety profile

Table 1: Tabulated summary of adverse events.

System organ class	**Frequency**	**Undesirable effect**	**Reference**
Infections and infestations	Less frequent	Candidiasis, flu syndrome, infection	

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Less frequent	Carcinoma, laryngeal neoplasia, skin carcinoma, gastric nodules, fundic polyps	
Blood and lymphatic system Disorders	Less frequent	Thrombocytopenia, anaemia, leucopenia, neutropenia, eosinophilia, haemolysis, lymphadenopathy, agranulocytosis, pancytopenia	
Immune system disorders	Less frequent	Allergic reaction, angioedema, anaphylactic shock	
Metabolic and nutrition disorders	Less frequent	Anorexia, gout, dehydration, hyperglycaemia/hypoglycaemia, peripheral oedema, weight gain/loss, hypomagnesaemia	
Psychiatric disorders	Less frequent	Agitation, anxiety, apathy, confusion, depersonalisation, depression, emotional lability, hallucinations, hostility aggravated, nervousness, neurosis, sleep disorder, thinking abnormality	
Nervous	Frequent	Headache, dizziness	

system disorders	Less frequent	Somnolence, insomnia, tremor, abnormal dreams, amnesia, convulsion, diplopia, hemiplegia, hyperkinesia, hypertonia, hypoesthesia, paraesthesia, vertigo, restlessness	
Eye Disorders	Less frequent	Blurred vision, abnormal vision, conjunctivitis, dry eyes, eye pain, photophobia, retinal degeneration, visual field defect, visual disturbances	
Ear and labyrinth disorders	Less frequent	Deafness, ear disorder, otitis media, tinnitus	
Cardiac disorders	Less frequent	Chest pain, angina, dysrrhythmia, bradycardia, myocardial infarction, palpitations, tachycardia, cardiospasm	
Vascular disorders	Less frequent	Oedema, cerebro vascular accident / cerebral infarction, hypertension / hypotension, migraine, shock (circulatory failure), syncope, vasodilation	

Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma, bronchitis, increased cough, dyspnoea, epistaxis, haemoptysis, hiccough, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/ infection, rhinitis, sinusitis, stridor, parosmia	
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, constipation, abdominal pain, flatulence, dry mouth or throat	
	Less frequent	Glossitis, taste abnormalities, ulcerative colitis, abdomen enlarged, halitosis, abnormal stools, bezoar, colitis, dyspepsia, dysphagia, enteritis, eructation, oesophageal stenosis, oesophageal ulcer, oesophagitis, faecal discolouration, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal haemorrhage, gum haemorrhage, haematemesis, increased appetite, increased salivation, melena, mouth ulceration, oral moniliasis, rectal disorder,	

		rectal haemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative stomatitis, taste loss, taste perversion, candidiasis of the oesophagus, pancreatitis	
	Frequency unknown	Collagenous colitis; Gastric glandularcysts	
Hepato-biliary disorders	Frequent	Increase in liver enzymes	
	Less frequent	Cholelithiasis, jaundice mostly with liver injury (increase in up to twice the upper limit of normal range of hepatic enzymes), hyper bilirubinaemia, hepatitis	
Skin and subcutaneous tissue disorders	Frequent	Skin rash, pruritus, urticaria	
	Less frequent	Alopecia, acne, contact dermatitis, dry skin, fixed eruption, hair disorder, macula papular rash, nail disorder, skin disorder, sweating, petechiae, purpura, erythema multiforme, photosensitivity, Steven-Johnson syndrome or toxic-epidermal necrolysis	

Musculoskeletal and connective tissue disorders	Less frequent	Arthralgia, myalgia, back pain, chills, neck pain, neck rigidity, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myasthenia, synovitis, fracture of the hip, wrist or spine	
Renal and urinary disorders	Less frequent	Dysuria, kidney calculus, kidney pain, polyuria, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, interstitial nephritis	
Reproductive system and breast disorders	Less frequent	Pelvic pain, libido decreased / increased, abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhoea, impotence, leukorrhoea, menorrhagia, menstrual disorder, penis disorder, testis disorder, vaginitis, gynaecomastia, galactorrhoea	
General disorders and administration site conditions	Frequent	Fatigue	
	Less frequent	Fever, malaise, pain, asthenia	

Investigations	Less frequent	Increase in cholesterol and triglyceride levels, hyponatraemia	

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 to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com

4.9 Overdose

Treatment is symptomatic and supportive. In the case of suspected overdose the patient should be monitored. Lansoprazole, as contained in **PRONIZOR 30 mg**, is not significantly eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

A.11.4.3 Medicines acting on the gastrointestinal tract.

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Lansoprazole is a specific proton pump (H, K-ATPase) inhibitor (PPI) of the gastric parietal cell. Lansoprazole inhibits gastric acid secretion in a dose related manner irrespective of the source of stimulation. Gastric secretory functions recover gradually following discontinuation of the medicine. Lansoprazole has no effect on histamine, gastrin or cholinergic receptors.

5.2 Pharmacokinetic properties

Absorption and distribution:

Absorption and distribution

Following oral administration, lansoprazole is well absorbed with a resultant bioavailability of approximately 78 %. The bioavailability is decreased if lansoprazole is taken with food. Peak serum concentrations are achieved approximately 1 to 2 hours following ingestion.

Metabolism

Lansoprazole is extensively metabolised via the hepatic cytochrome P450 system to the inactive, sulfated metabolites, sulphone, sulphide and 5- hydroxyl lansoprazole. The half-life for lansoprazole is 1,4 to 1,5 hours. This does not alter during treatment.

Elimination:

Lansoprazole is totally eliminated after oral administration. The main route of elimination is via the bile with 15 to 30 % of lansoprazole being excreted via the kidneys as the hydroxylated metabolite.

Special populations

Geriatric

The clearance of lansoprazole is decreased in the elderly; with the elimination half-life increased approximately 50 to 100 %. Because the mean half-life in the elderly remains between 1,9 to 2,9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly.

Hepatic impairment

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole is prolonged from 1,5 hours to 3,2 to 7,2 hours. An increase in mean AUC up to 500 % is observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (20 - 25 mesh ASTM), Ethyl cellulose, Hypromellose 2910 (Methocel E5 premium LV), Methylene chloride, Isopropyl alcohol, Magnesium carbonate heavy, Low substituted hydroxypropyl cellulose (LH 31), Maize starch, Talc, Polyethylene glycol (Polyglycol 6000 PF), Methacrylic acid copolymer dispersion (Eudragit L 30D 55, Titanium dioxide (Kronos 1171), Polysorbate 80 Tween 80 HP- LQ- (MH), Colloidal silicon dioxide (Aerosil 200)

Composition of inactive ingredients (Capsule):

Cap: Gelatin, Water, FD & C Blue 1 (E 133), D & C Red 28, FD & C Red 40 (E 129), Titanium Dioxide (E 171)

Body: Gelatin, Water, FD & C Green 3 (E143) for 15 mg and FD & C Red 40 (E129) for 30 mg, Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the date of manufacture

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

~~KEEP OUT OF REACH OF CHILDREN~~

6.5 Nature and contents of container

PRONIZOR 30 mg

HDPE Container Pack (28's and 30's):

Round, white, HDPE container, 60cc, 33 mm screw neck, with 33 mm child resistant closure with pulp and HS 123 white printed liner and silica gel sachet 1g (2 Nos.) as a desiccant.

Blister pack (2's, 4's, 7's ,14's and 28's):

Cold form laminate as forming material: 25µ OPA/ 45µ Aluminium / 60µ PVC and Aluminium foil as lidding material:Plain 30µ Aluminum Foil/ 6 - 8 gsm HSL

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

Contact details: safety@macleodspharma.com

0116821169

8. REGISTRATION NUMBERS

PRONIZOR 30 mg 52/11.4.3/0359

9. DATE OF FIRST AUTHORISATION

13 September 2022

10. DATE OF REVISION OF THE TEXT