PACKAGE INSERT FOR

LANSOLOC 30 CAPSULES

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

LANSOLOC 30 (Capsules)

COMPOSITION:

Each **LANSOLOC 30** capsule contains 30 mg of lansoprazole.

Inactive ingredients are colloidal anhydrous silica, colourants, gelatine, hydroxypropylcellulose, hypromellose, light magnesium carbonate, maize starch, methacrylic acid copolymer, polyethylene glycol, polysorbate 80, povidone, purified talc, sodium hydroxide, sodium lauryl sulphate, sucrose, sugar spheres and titanium dioxide.

Contains sugar: Sucrose (37,8 mg).

PHARMACOLOGICAL CLASSIFICATION:

A 11.4.3 Antacids – Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lansoprazole is a specific inhibitor of the gastric H^+ K^+-ATPase (proton pump) of the gastric parietal cell that inhibits the terminal step in acid production.

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.

Pharmacokinetic properties:

Absorption and distribution:

As lansoprazole is unstable in acid, it is administered orally in the form of enteric-coated granules in capsules.

Following oral administration, lansoprazole is well absorbed with a resultant bioavailability of approximately 78 %. Pharmacokinetic parameters revealed no statistically significant differences between day 1 and day 7 after repeated doses with regard to C_{max}, T_{max}, AUC (area under the concentration-time curve), or half-life.

The bioavailability is decreased if lansoprazole is taken with food. As an acidic pH in the parietal cell acid canaliculi is required for activation, and since food stimulates acid production, lansoprazole should be taken about 30 minutes before meals.

Peak serum concentrations are achieved approximately 1,5 hours following ingestion.

Lansoprazole is highly protein bound (97 %).

Metabolism:

Lansoprazole is metabolised mainly in the liver. Lansoprazole is extensively metabolised via the hepatic cytochrome P450 system to the inactive, sulphated metabolites – sulphone, sulphide and 5-hydroxylansoprazole. These metabolites do not have notable activity or toxicity. The plasma elimination 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 – 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 elimination half-life increased approximately 50 – 100 %. Because the mean half-life in the elderly remains between 1,9 – 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.

Renal insufficiency:

In patients with severe renal insufficiency, plasma protein binding decreased by 1,0 – 1,5 % after administration of 60 mg of lansoprazole. Patients with renal insufficiency has a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, is not related to the degree of renal impairment and C_{max} and T_{max} is not different from subjects with healthy kidneys. No

dosage adjustment is necessary in patients with renal insufficiency (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Hepatic insufficiency:

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 – 7,2 hours. An increase in mean AUC of up to 500 % was observed at steady-state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered (see **"CONTRAINDICATIONS"**).

INDICATIONS:

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

CONTRAINDICATIONS:

- Hypersensitivity to lansoprazole or to any of the ingredients of **LANSOLOC 30**.
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).
- Liver impairment.
- Co-administration with atazanavir, due to a significant reduction in atazanavir exposure (see **"INTERACTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

Safety and efficacy in children has not been established.

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 **LANSOLOC 30** may alleviate symptoms and delay diagnosis.

Therefore, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded prior to treatment with **LANSOLOC 30**, particularly in patients of middle age or older, who have new or recently changed dyspeptic symptoms.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

LANSOLOC 30 is not indicated for mild gastrointestinal complaints, such as nervous dyspepsia.

Hypomagnesaemia

In patients treated with **LANSOLOC 30** for at least three months, and in most cases for a year, severe hypomagnesaemia has been reported. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur, but they may begin insidiously and be overlooked. Discontinuation of **LANSOLOC 30** and magnesium replacement will improve hypomagnesaemia in most affected patients.

For patients expected to be on prolonged treatment or who take **LANSOLOC 30** with digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), healthcare

professionals should consider measuring magnesium levels before starting **LANSOLOC 30** treatment and periodically during treatment.

Bone fractures:

Proton pump inhibitors, such as **LANSOLOC 30**, especially if used in high doses and over extended periods of time (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, mainly in the elderly or where other recognised risk factors are present. Observational studies have suggested that proton pump inhibitors, such as **LANSOLOC 30** may increase the overall risk of fracture by 10 – 40 %. Patients who are at risk of osteoporosis should have a sufficient intake of vitamin D and calcium and receive care according to current clinical guidelines.

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.

If a patient develops persistent diarrhoea, administration of **LANSOLOC 30** should be discontinued due to the possibility of microscopic colitis with thickening of the collagen bundle, or infiltration of inflammatory cells noted in the large intestine submucosa. In the majority of cases, symptoms of microscopic colitis resolve on discontinuation of **LANSOLOC 30**.

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

gastrointestinal infections, such as with *Salmonella* and *Campylobacter* (see **"SIDE-EFFECTS"**).

LANSOLOC 30 may also 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.

Patients should use the lowest dose and shortest duration of **LANSOLOC 30** therapy appropriate to the condition being treated.

CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents indicated for use in combination with **LANSOLOC 30**, refer to the package inserts of these respective medicines.

Treatment with **LANSOLOC 30** may cause false-negative results in the urea breath test for *Helicobacter pylori* infection. The manufacturers of the urea breath test for *H. pylori* recommend that it should not be performed for at least 2 weeks after stopping treatment with **LANSOLOC 30**.

Tubulointerstitial nephritis:

The risk of tubulointerstitial nephritis leading to chronic renal inflammation and reduced renal function is associated with the use of PPI's. Tubulointerstitial nephritis may progress to renal failure as is it not necessarily reversed when treatment is discontinued.

Special warnings about other ingredients*:*

Each **LANSOLOC 30** capsule contains sugar/sucrose; therefore, **LANSOLOC 30** is not suitable for patients with inborn fructose intolerance, with glucose-galactose malabsorption syndrome or sucrose isomaltase deficiency.

Effects on ability to drive and operate machinery*:*

LANSOLOC 30 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.

INTERACTIONS:

Since **LANSOLOC 30** is metabolised through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes, the possibility exists for interactions with medicines that are metabolised via this system.

When administering **LANSOLOC 30** with the CYP2C19 inhibitor fluvoxamine, a dose reduction may be considered as plasma concentrations of **LANSOLOC 30** increases up to 4-fold.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John's wort (*Hypericum perforatum)* can significantly reduce the plasma concentrations of **LANSOLOC 30.**

Studies have shown that **LANSOLOC 30** does not have clinically significant interactions with other medicines metabolised by the cytochrome P450 system, such as antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam or clarithromycin, in healthy subjects. These medicines are metabolised through various cytochrome P450 isozymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

When **LANSOLOC 30** was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10 %) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when **LANSOLOC 30** is started, or stopped, to ensure clinically effective blood levels.

Concomitant use of proton pump inhibitors such as **LANSOLOC 30** may elevate and prolong serum levels of methotrexate and/or its metabolites, possibly leading to methotrexate toxicities. It is recommended that in high-dose methotrexate administration, temporary withdrawal of **LANSOLOC 30** may be considered.

Concomitant use of **LANSOLOC 30** and tacrolimus increases the plasma concentrations of tacrolimus (a CYP3A and Pgp substrate). **LANSOLOC 30** exposure increases the mean exposure of tacrolimus by up to 81 %. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with **LANSOLOC 30** is initiated or ended.

There have been reports of increased International Normalised Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including **LANSOLOC 30**, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with **LANSOLOC 30** and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Caution should be exercised when oral contraceptives and carbamazepine are taken concomitantly with **LANSOLOC 30**.

LANSOLOC 30 has been shown to have no clinically significant interaction with amoxicillin, or non-steroidal anti-inflammatory drugs (NSAIDs).

Sucralfate delays absorption of proton pump inhibitors and reduces the bioavailability of single-dose lansoprazole 30 mg by 17 % when administered concomitantly. Therefore, **LANSOLOC 30** should be taken at least 30 minutes prior to sucralfate.

Antacids may reduce the bioavailability of **LANSOLOC 30** and should not be taken within 1 hour of a dose of **LANSOLOC 30**.

LANSOLOC 30 causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that **LANSOLOC 30** may interfere with the absorption of medicines where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, itraconazole, voriconazole, ampicillin esters, iron

salts, digoxin, and dasatinib). With voriconazole, the plasma concentration of both medicines may be increased.

Since there is a report of a significant reduction in atazanavir exposure when **LANSOLOC 30** is concomitantly administered, **LANSOLOC 30** should not be co-administered with atazanavir (see **"CONTRAINDICATIONS"**).

PREGNANCY AND LACTATION:

LANSOLOC 30 is contraindicated during pregnancy and lactation (see **"CONTRAINDICATIONS"**).

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

It is not known whether lansoprazole, as in **LANSOLOC 30**, is distributed into breast milk. However, lansoprazole or its metabolites are distributed into the milk of rats and has been shown to cause tumorigenic effects in animals.

DOSAGE AND DIRECTIONS FOR USE:

The recommended once daily dosage of **LANSOLOC 30** should be preferably taken before a meal, in the morning.

The capsules should be swallowed whole. Do not crush or chew.

Gastric ulcer:

30 mg once a day for up to eight weeks.

Duodenal ulcer:

30 mg once a day for up to four weeks.

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

Oesophagitis due to gastro-oesophageal reflux:

30 mg once a day for four weeks. Depending on the endoscopic results, a repeat course of 4 weeks may be necessary.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

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.

SIDE-EFFECTS:

The most frequently reported adverse events with **LANSOLOC 30** are headache, dizziness, fatigue, and malaise.

Infections and infestations:

Less frequent:	Candidiasis, infection, oral moniliasis, pneumonia, upper respiratory infection, urinary tract infection.
Frequency unknown:	*Clostridium difficile* associated diarrhoea.

Neoplasms, benign and malignant (including cysts and polyps):

Less frequent:	Carcinoma, laryngeal neoplasia, skin carcinoma.

Blood and lymphatic system disorders:

Less frequent:	Thrombocytopenia, anaemia, leukopenia, neutropenia, eosinophilia, haemolysis, lymphadenopathy, agranulocytosis, pancytopenia.
Frequency unknown:	Bruising, purpura, petechiae.

Immune system disorders:

Less frequent:	Allergic reaction.
Frequency unknown:	Hypersensitivity reactions, including angioedema, wheezing (bronchospasm), anaphylaxis, and fever.

Endocrine disorders:

Less frequent:	Diabetes mellitus, goitre, hypothyroidism.

Metabolism and nutrition disorders:

Less frequent:	Anorexia, increased appetite, thirst, gout, dehydration, hyperglycaemia or hypoglycaemia, weight gain or loss.
Frequency unknown:	Hyponatraemia, hypomagnesaemia.

Psychiatric disorders:

Less frequent:	Insomnia, somnolence, abnormal dreams, agitation, anxiety, apathy, depersonalisation, depression, emotional lability, hallucinations, aggravated hostility, increased or decreased libido, nervousness, neurosis, sleep disorder, thinking abnormality.

Nervous system disorders:

Frequent:	Headache.
Less frequent:	Cerebrovascular accident, cerebral infarction, migraine, amnesia, confusion, convulsion, hemiplegia, hyperkinesia, hyperaesthesia, paraesthesia, parosmia, taste loss, taste perversion, dizziness, tremor.

Eye disorders:

Less frequent:	Blurred vision, diplopia, abnormal vision, conjunctivitis, dry eyes, eye pain, photophobia, retinal degeneration, visual field defect.

Ear and labyrinth disorders:

Less frequent: Vertigo, deafness, ear disorder, otitis media, tinnitus.

Cardiac disorders:

Less frequent: Angina, myocardial infarction, dysrhythmia, bradycardia, palpitations, tachycardia, syncope.

Vascular disorders:

Less frequent: Oedema, hypertension, hypotension, shock (circulatory failure), vasodilation, peripheral oedema.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Asthma, bronchitis, increased cough, dyspnoea, epistaxis, haemoptysis, hiccup, pharyngitis, pleural disorder, respiratory disorder, upper respiratory inflammation, rhinitis, sinusitis, stridor.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, constipation, abdominal pain.

Less frequent: Dry mouth, glossitis, ulcerative colitis, enlarged abdomen, halitosis, abnormal stools, bezoar,

	cardiospasm (oesophageal pain), colitis, dyspepsia, dysphagia, enteritis, eructation, oesophageal stenosis, oesophageal ulcer, oesophagitis, faecal discolouration, flatulence, gastric nodules or fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal haemorrhage, gum haemorrhage, haematemesis, increased salivation, melaena, mouth ulceration, rectal disorder, rectal haemorrhage, stomatitis, tenesmus, tongue disorder, ulcerative stomatitis.
Frequency unknown:	Sore mouth or throat.

Hepato-biliary disorders:

Less frequent:	Cholelithiasis, elevation in hepatic enzymes, jaundice [mostly in association with liver injury (an increase in up to twice the upper limit of the normal range of hepatic enzymes)], hyperbilirubinaemia, hepatitis.
Frequency unknown:	Hepatic failure, hepatic encephalopathy.

Skin and subcutaneous tissue disorders:

Frequent:	Skin rash, pruritus, urticaria.
Less frequent:	Alopecia, acne, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail

	disorder, skin disorder, sweating, Stevens-Johnson syndrome, or toxic epidermal necrolysis.
Frequency unknown:	Erythematous or bullous rashes, including erythema multiforme, hair thinning, photosensitivity.

Musculoskeletal, connective tissue and bone disorders:

Less frequent:	Arthralgia, myalgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myasthenia, synovitis, fractures of the hip, wrist or spine.

Renal and urinary disorders:

Less frequent:	Dysuria, kidney calculus, kidney pain, polyuria, urethral pain, urinary frequency, urinary urgency, urination impaired, interstitial nephritis (with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued).

Reproductive system and breast disorders:

Less frequent:	Gynaecomastia, galactorrhoea, abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhoea, impotence,

	leucorrhoea, menorrhagia, menstrual disorder, penis disorder, testis disorder, vaginitis.

General disorders and administrative site conditions:

Less frequent:	Asthenia, fever, back pain, chest pain, chills, flu syndrome, malaise, neck pain, neck rigidity, pain, pelvic pain.
Frequency unknown:	Fatigue.

Post-marketing exposure:

Frequency unknown:	Interstitial nephritis with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See "**SIDE-EFFECTS".**

Apart from symptomatic treatment, no specific therapeutic recommendation can be made in cases of overdosage.

Treatment is symptomatic and supportive.

IDENTIFICATION:

White to off-white, enteric-coated pellets in hard gelatine capsule shells, size ‘1’, with red cap and white body.

PRESENTATION:

White HDPE container of 14 and 28 capsules or outer carton containing an aluminium foil blister strip of 10 capsules, packed in 30’s.

STORAGE INSTRUCTIONS:

Store in a cool, dry place, at or below 25 ºC.

Protect from light. Keep the blisters in the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

37/11.4.3/0155

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Parc du Cap

Mispel Street

Bellville

7530

DATE OF PUBLICATION OF PACKAGE INSERT:

17 September 2004

Revised: 03 February 2021