Proposed Professional Information – Clean Copy

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

RAN-LANSOPRAZOLE 15 (Capsules)

RAN-LANSOPRAZOLE 30 (Capsules)

COMPOSITION

RAN-LANSOPRAZOLE 15

Each capsule contains:

Lansoprazole 15 mg

Sugar (sucrose) 80 mg

RAN-LANSOPRAZOLE 30

Each capsule contains:

Lansoprazole 30 mg

Sugar (sucrose) 160 mg

Excipients: Colloidal anhydrous silica, empty hard gelatin capsule shell, hydroxypropyl methyl cellulose, macrogol 300, methacrylic acid-ethylacrylate copolymer (1:1) dispersion 30 %, purified talc, purified water and titanium dioxide.
Contains sugar: sucrose.

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on the gastro-intestinal tract

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

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 1-2 hours following ingestion.

Lansoprazole is highly protein bound (97 %).

Lansoprazole is extensively metabolised via the hepatic cytochrome P450 system to the inactive, sulphated metabolites – sulphone, sulphide and 5-hydroxyllansoprazole. The half life for lansoprazole is 1,4 to 1,5 hours.

The main route of elimination is via the bile with 15-30 % of lansoprazole being excreted via the kidneys as the hydroxylated metabolite.

INDICATIONS

RAN-LANSOPRAZOLE 30 is indicated for the short-term treatment of gastric and duodenal ulcers and reflux oesophagitis.

RAN-LANSOPRAZOLE 15 is indicated in the short-term management of mild functional dyspepsia and for the prevention of relapse of gastro-oesophageal reflux.

RAN-LANSOPRAZOLE 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 other ingredients of **RAN-LANSOPRAZOLE**.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

Severe liver impairment.

RAN-LANSOPRAZOLE should not be co-administered with atazanavir and nelfinavir due to significant reduction in atazanavir exposure (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

Safety and efficacy in children has not been established.

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

RAN-LANSOPRAZOLE should be used with caution in patients with liver impairment (see **CONTRAINDICATIONS**).

In patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as a[n] aetiological factor should be considered. If **RAN-LANSOPRAZOLE** is used in combination with antibiotics for eradication therapy of *H.pylori,* then the instructions for the use of these antibiotics should also be followed.

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and a thorough risk/benefit assessment should regularly be performed in these patients.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

RAN-LANSOPRAZOLE is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

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

Proton pump inhibitors, such as **RAN-LANSOPRAZOLE**, especially if used in high doses and over long durations (>1 year), may increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines.

Decreased gastric acidity increases gastric counts of bacteria normally present in the gastro-intestinal tract. Treatment with **RAN-LANSOPRAZOLE** may lead to an increased risk of gastro-intestinal infections such as *Salmonella* and *Campylobacter*.

Proton pump inhibitor (PPI) therapy like **RAN-LANSOPRAZOLE** 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.

Proton pump inhibitors, such as lansoprazole as in **RAN-LANSOPRAZOLE**, are associated with subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-

exposed areas of the skin, and if accompanied by arthralgia, the medical practitioner should consider stopping **RAN-LANSOPRAZOLE**.

Proton pump inhibitors, such as lansoprazole as in **RAN-LANSOPRAZOLE**, are associated with an increased risk of subclinical acute or chronic interstitial nephritis associated with proton pump inhibitors (PPIs) leading to chronic renal inflammation and reduced renal function. Interstitial nephritis may progress to renal failure as it is not necessarily reversed when treatment is discontinued.

Patients should use the lowest dose and shortest duration of **RAN-LANSOPRAZOLE** therapy appropriate to the condition being treated.

Effects on ability to drive or operate machines

Adverse reactions such as dizziness, vertigo, visual disturbances and somnolence may occur (see **SIDE EFFECTS**). Under these conditions the ability to react may be decreased. 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.

Sucrose

RAN-LANSOPRAZOLE contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take **RAN-LANSOPRAZOLE**.

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with **RAN-LANSOPRAZOLE** and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Concomitant administration of PPIs such as **RAN-LANSOPRAZOLE** and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of **RAN-LANSOPRAZOLE** may be considered in some patients.

Medicines with pH dependent absorption

RAN-LANSOPRAZOLE may interfere with the absorption of medicines where gastric pH is critical to bioavailability.

- *Atazanavir:* A study has shown that co-administration of lansoprazole (60 mg once daily) with atazanavir 400 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 90 % decrease in AUC and C_{max}). **RAN-LANSOPRAZOLE** should not be co-administered with atazanavir (see **CONTRAINDICATIONS**).

- *Ketoconazole and itraconazole:* The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of **RAN-LANSOPRAZOLE** may result in sub-therapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

- *Digoxin:* Co-administration of **RAN-LANSOPRAZOLE** 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 **RAN-LANSOPRAZOLE** treatment.

- **RAN-LANSOPRAZOLE** may interfere with the absorption of other medicines where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, iron salts).

Medicines metabolised by P450 enzymes

Lansoprazole may increase plasma concentrations of medicines that are metabolised by CYP3A4. Caution is advised when combining **RAN-LANSOPRAZOLE** with medicines which are metabolised by this enzyme and have a narrow therapeutic window.

- *Theophylline:* Lansoprazole reduces the plasma concentration of theophylline, which may decrease the expected clinical effect at the dose. Caution is advised when combining the two medicines.

- *Tacrolimus:* Co-administration of lansoprazole increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Lansoprazole exposure increased the mean exposure of tacrolimus by up to 81 %. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with **RAN-LANSOPRAZOLE** is initiated or ended.

Medicines which inhibit CYP2C19

- *Fluvoxamine:* A dose reduction may be considered when combining lansoprazole with the CYP2C19 inhibitor fluvoxamine. A study shows that the plasma concentrations of lansoprazole increase up to 4-fold.

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.

Others

- *Sucralfate/Antacids:* Sucralfate/Antacids may decrease the bioavailability of lansoprazole. Therefore **RAN-LANSOPRAZOLE** should be taken at least 1 hour after taking these medicines.

- No clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory medicines have been demonstrated, although no formal interactions studies have been performed.

Clopidogrel: Concomitant administration of lansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of **RAN-LANSOPRAZOLE**.

PREGNANCY AND LACTATION

RAN-LANSOPRAZOLE is contraindicated in pregnancy and lactation.

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

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 nursing should be discontinued or the medicine withdrawn, taking into account the importance of lansoprazole to the mother (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

RAN-LANSOPRAZOLE should be preferably taken before a meal.

Gastric ulcer:

30 mg once a day for up to eight weeks.

Duodenal ulcer:

30 mg once a day for up to four weeks.

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

Maintenance treatment for the prevention of gastro-oesophageal reflux:

15 mg once a day for a maximum period of one year.

Functional dyspepsia:

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

Elderly:

No dose adjustment is necessary. However, 30mg 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

Infections and Infestations:

Unknown frequency: Clostridium difficile associated diarrhoea.

Blood and lymphatic system disorders:

Less frequent: Thrombocytopenia, anaemia, leucopenia, neutropenia, eosinophilia, agranulocytosis, pancytopenia, haemolysis, lymphadenopathy.

Unknown frequency: Aplastic anaemia, haemolytic anaemia, thrombotic thrombocytopenic purpura.

Immune system disorders:

Less frequent: Allergic reaction, anaphylactic shock, angioedema.

Endocrine disorders:

Less frequent: Diabetes mellitus, goitre, hypothyroidism.

Metabolism and nutritional disorders

Less frequent: Avitaminosis, gout, dehydration, hyperglycaemia/hypoglycaemia, peripheral oedema, weight gain/loss.

Unknown frequency: Hypomagnesaemia (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Psychiatric disorders

Less frequent: Depression, insomnia, hallucination, confusion, abnormal dreams, agitation, aggression, amnesia, anxiety, apathy, convulsion, dementia, epersonalisation, emotional lability, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, libido decreased/increased, nervousness, neurosis, sleep disorder, thinking abnormality, parosmia, speech disorder.

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Somnolence, tremor, restlessness, vertigo, paraesthesia, increased sweating.

Eye disorders:

Less frequent: Blurred vision, visual disturbances, abnormal vision, diplopia, amblyopia, blepharitis, cataract, conjunctivitis, dry eyes, eye disorder, eye pain, glaucoma, photophobia, retinal degeneration/disorder, visual field defect.

Ear disorders:

Less frequent: Deafness, ear disorder, otitis media, tinnitus.

Cardiac disorders:

Less frequent: Angina, dysrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, cardiospasm, chest pain.

Vascular disorders:

Less frequent: Migraine, vasodilation.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Asthma, bronchitis, bronchospasm, increased cough, dyspnoea, epistaxis, haemoptysis, hiccup, laryngeal neoplasia, lung fibrosis, pharyngitis, pleural disorder,

pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, constipation and abdominal pain, flatulence, dry mouth or throat.

Less frequent: Glossitis, taste abnormalities, taste loss, colitis, candidiasis of the oesophagus, pancreatitis, stomatitis, anorexia, abdomen enlarged, abnormal stools, bezoar, cholelithiasis, dyspepsia, dysphagia, enteritis, eructation, oesophageal stenosis, oesophageal ulcer, oesophagitis, faecal discolouration, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal haemorrhage, gum haemorrhage, haematemesis, increased appetite, increased salivation, melaena, mouth ulceration, gastrointestinal moniliasis, rectal disorder, rectal haemorrhage, tenesmus, thirst, tongue disorder, ulcerative stomatitis, halitosis.

Hepatobiliary disorders:

Frequent: Increase in liver enzyme levels.

Less frequent: Hepatitis, jaundice.

Unknown frequency: Hepatotoxicity, hepatic failure or necrosis.

Skin and subcutaneous tissue disorders:

Frequent: Skin rash, pruritus, urticaria.

Less frequent: Alopecia, petechiae, purpura, erythema multiforme, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, acne, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, skin carcinoma, skin disorder, peripheral oedema, subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders:

Less frequent: Asthenia, arthralgia, myalgia, fracture of the hip, wrist or spine (see **WARNINGS AND SPECIAL PRECAUTIONS**), arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myasthenia, ptosis, synovitis, back pain, neck pain, neck rigidity.

Renal and urinary disorders

Less frequent: Interstitial nephritis, dysuria, kidney calculus, kidney pain, polyuria, urethral pain, urinary frequency, urinary retention, urinary tract infection, urinary urgency, urination impaired.

Reproductive system and breast disorders

Less frequent: Gynaecomastia, galactorrhoea, abnormal menses, menorrhagia, menstrual disorder, breast enlargement, breast pain, breast tenderness, dysmenorrhoea, impotence, pelvic pain, penis disorder, testis disorder, leukorrhoea, vaginitis.

General disorders and administration site conditions:

Frequent: Fatigue.

Less frequent: Fever, oedema, hyperhidrosis, carcinoma, chills, flu syndrome, infection, malaise, pain.

Investigations

Less frequent: Increase in cholesterol and triglyceride levels, hyponatraemia.

Unknown frequency: Increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinaemia, increased blood potassium, increased blood urea, crystal urine present, decreased haemoglobin, increased/ decreased electrolytes, increased glucocorticoids, increased LDH, increased/ decreased/ abnormal platelets, increased gastrin levels and positive faecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and haematuria were also reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **SIDE EFFECTS**.

The effects of overdose on lansoprazole in humans are not known.

In the case of suspected overdose the patient should be monitored. Lansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

Treatment is symptomatic and supportive.

IDENTIFICATION

RAN-LANSOPRAZOLE 15: Yellow cap/yellow body, self locked hard gelatin capsule of size '3' imprinted with 'L 15' on both cap and body containing white to off-white pellets.

RAN-LANSOPRAZOLE 30: Purple cap/lavender body, self locked hard gelatin capsule of size '1' imprinted with 'L 30' on both cap and body containing white to off-white pellets.

PRESENTATION

7 capsules are packed in cold form blister strips or aluminium strips.

Cold form blister strips comprise of a cold form laminate with a backing of aluminium foil sealed with a heat seal lacquer.

Aluminium strips comprise of aluminium foil laminated with low-density polyethylene.

Cartons contain 7, 14 or 28 capsules.

STORAGE INSTRUCTIONS

Store at or below 25 ^{0}C, in the original container protected from light and moisture.

Do not remove blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

RAN-LANSOPRAZOLE 15: A39/11.4.3/0251

RAN-LANSOPRAZOLE 30: A39/11.4.3/0252

NAME AND BUSSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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