1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ASPEN LANSOPRAZOLE 15 (capsules)

ASPEN LANSOPRAZOLE 30 (capsules)

COMPOSITION

Each ASPEN LANSOPRAZOLE 15 capsule contains lansoprazole 15 mg.

Each ASPEN LANSOPRAZOLE 30 capsule contains lansoprazole 30 mg.

ASPEN LANSOPRAZOLE 15:

Excipients:

Brilliant blue (C.I. 42090), colloidal silicon dioxide, erythrosine (C.I. 45430), gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, maize starch, methacrylic acid co-polymer, methyl paraben, polyethylene glycol, polysorbate, povidone, propylparaben, purified talc, sugar, titanium dioxide (C.I. 77891)

Preservatives:

Methyl paraben 0,12 % *m/m*, propyl paraben 0,03 % *m/m*

Contains sugar: Sucrose 94,00 mg

ASPEN LANSOPRAZOLE 30:

Excipients:

Bronopol, carmoisine, colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, maize starch, methacrylic acid co-polymer, polyethylene glycol, polysorbate, Ponceau 4R, povidone, purified talc, sodium lauryl sulphate, sugar, sunset yellow, titanium dioxide

Preservative:

Bronopol 0,01 % *m/m*

Contains sugar: Sucrose 188,00 mg

PHARMACOLOGICAL CLASSIFICATION

A.11.4.3 Medicines acting on the gastrointestinal tract.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

Pharmacokinetic properties

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.

Lansoprazole is highly protein bound (97 %).

Metabolism

Lansoprazole is extensively metabolised via the hepatic cytochrome P450 system to the inactive, sulfated metabolites, sulphone, sulphide and 5- hydroxyllansoprazole. 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.

Renal impairment

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

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.

INDICATIONS

- ASPEN LANSOPRAZOLE 15 and 30 is indicated for the short-term treatment of active duodenal ulcers and reflux oesophagitis.
- ASPEN LANSOPRAZOLE is indicated for *Helicobacter pylori*-positive duodenal ulcers in conjunction with appropriate antibiotics as part of an eradication program.
- ASPEN LANSOPRAZOLE 30 is indicated for the short-term treatment of gastric ulcer.
- ASPEN LANSOPRAZOLE 15 is indicated for the short-term management of mild functional dyspepsia and for the prevention of relapse of gastro-oesophageal reflux.

CONTRAINDICATIONS

ASPEN LANSOPRAZOLE is contraindicated in:

- Patients with hypersensitivity to lansoprazole or to any of the other ingredients contained in ASPEN LANSOPRAZOLE (see COMPOSITION).
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- Liver impairment.

- ASPEN LANSOPRAZOLE should not be used concomitantly with atazanavir and nelfinavir (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

Children

Safety and efficacy in children has not been established.

Malignant disease

Treatment with ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE.

Malabsorption

Proton pump inhibitors such as ASPEN LANSOPRAZOLE have been reported to result in a substantial reduction in cyanocobalamin (Vitamin B_{12}) absorption, probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy. Uk licensed product information recommends that severely ill children, who may have borderline body stores of cyanocobalamin, should have serum vitamin B_{12} concentratins monitored if they require long-term therapy. Proton pump inhibitors such as ASPEN LANSOPRAZOLE have also been reported to impair the bioavailability of dietary vitamin C. Fat malabsorbtion, secondary to increased deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with proton pump inhibitors such as ASPEN LANSOPRAZOLE treatment. For the suggestion that proton pump inhibitors such as ASPEN LANSOPRAZOLE can cause calcium malabsorption, see Effects on the Musculoskeletal Sytem.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors such as ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE. SCLE after previous treatment with a proton pump inhibitor such as ASPEN LANSOPRAZOLE may increase the risk of SCLE with other proton pump inhibitors.

Alcohol and CNS depressants

ASPEN LANSOPRAZOLE 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 ASPEN 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. Other serious events include tremors, carpo-pedal spasm, atrial fibrillation, supraventricular tachycardia, and abnormal QT interval. Hypomagnesaemia also produces impaired parathyroid hormone secretion which may lead to hypocalcaemia. 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 ASPEN LANSOPRAZOLE with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting ASPEN LANSOPRAZOLE treatment and periodically during treatment.

Bone fracture

PPIs like lansoprazole, as contained in ASPEN LANSOPRAZOLE, 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 ASPEN LANSOPRAZOLE has been linked to an increased risk of enteric infections such as CDAD. A diagnosis of CDAD should be considered for patients taking ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE 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 occured in patients taking lansoprazole as contained in ASPEN LANSOPRAZOLE. Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.

Effects on ability to drive and use machines

ASPEN LANSOPRAZOLE 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.

Excipients

Contains sucrose.

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

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ASPEN LANSOPRAZOLE.

INTERACTIONS

Effects of ASPEN LANSOPRAZOLE on other medications

Medicines with pH dependent absorption

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

HIV medications

ASPEN LANSOPRAZOLE should not be used with atazanavir or nelfinavir, as it substantially reduces exposure to the HIV-protease inhibitor (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 ASPEN LANSOPRAZOLE may result in sub-therapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

Digoxin

Co-administration of ASPEN 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 ASPEN LANSOPRAZOLE treatment.

Medicines metabolised by P450 enzymes

ASPEN LANSOPRAZOLE may increase plasma concentrations of medicines that are metabolised by CYP3A4. Caution is advised when combining ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE. Patients may require additional titration of their theophylline dosage when ASPEN LANSOPRAZOLE is started or stopped to ensure clinically effective blood levels.

Tacrolimus

Co-administration of ASPEN LANSOPRAZOLE increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE

Medicines which inhibit CYP2C19

Fluvoxamine

A dose reduction may be considered when combining ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE .

Others

Warfarin

Monitoring of patients receiving concomitant warfarin is recommended. Increased INR and prothrombin time in patients receiving ASPEN LANSOPRAZOLE 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 ASPEN LANSOPRAZOLE may be decreased with concomitant administration of sucralfate/antacids. ASPEN LANSOPRAZOLE should be taken at least 1 hour after taking these medications.

Methotrexate

Lansoprazole as contained in ASPEN LANSOPRAZOLE has been reported not to affect the pharmacokinetics of methotrexate.

PREGNANCY AND LACTATION

ASPEN LANSOPRAZOLE in contraindicated in pregnancy and lactation (see CONTRAINDICATIONS).

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 ASPEN LANSOPRAZOLE to the mother.

DOSAGE AND DIRECTIONS FOR USE

ASPEN LANSOPRAZOLE should preferably be taken before a meal.

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.

ASPEN LANSOPRAZOLE 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.

Maintenance treatment for the prevention of gastro-oesophageal reflux:

One 15 mg capsule once a day for a maximum period of one year. No clinical information is available for treatment longer than one year.

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.

SIDE EFFECTS

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 polyos

Blood and the lymphatic system disorders

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

Immune system disorders

Less frequent: Allergic reaction, angioedema, anaphylactic shock

Metabolism 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 system disorders

Frequent: Headache, dizziness

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, cerebrovascular 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 glanducer cytes

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), hyperbilirubinaemia, hepatitis

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, petechiae, purpura, erythema multiforme, photosensitivity, Steven-Johnson syndrome or toxic-epidermal necrolysis

Musculoskeletal, connective tissue and bone 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 administrative site conditions

Frequent: Fatigue

Less frequent: Fever, malaise, pain, asthenia

Investigations

Less frequent: Increase in cholesterol and triglyceride levels, hyponatraemia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See SIDE EFFECTS)

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

IDENTIFICATION

ASPEN LANSOPRAZOLE 15:

White to off-white, enteric-coated pellets in hard gelatin capsule shells, size “3”, with blue cap and white body.

ASPEN LANSOPRAZOLE 30:

White to off-white, enteric-coated pellets in hard gelatin capsule shells, size “1”, with red cap and white body.

PRESENTATION

ASPEN LANSOPRAZOLE 15:

7, 14 or 28 capsules are packed in a white high density polyethylene container with a white high density polyethylene cap and a natural low density polyethylene plug, together with a silica gel bag. The container is packed into an outer cardboard carton.

7, 14 or 28 capsules are packed in a polyvinylchloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton.

ASPEN LANSOPRAZOLE 30:

14 or 28 capsules are packed in a white high density polyethylene container with a natural low density polyethylene plug and a white high density polyethylene cap, together with a silica gel bag. The container is packed into an outer cardboard carton.

14 or 28 capsules are packed in a polyvinylchloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

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

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ASPEN LANSOPRAZOLE 15: 37/11.4.3/0237

ASPEN LANSOPRAZOLE 30: 37/11.4.3/0154

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

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration:

ASPEN LANSOPRAZOLE 15 mg: 13 February 2013

ASPEN LANSOPRAZOLE 30 mg: 27 November 2009

Date of the most recently revised approved package insert:

ASPEN LANSOPRAZOLE 15 mg: 25 May 2020

ASPEN LANSOPRAZOLE 30 mg: 25 May 2020

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