For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

(Pantoprazole sodium 40 mg And Levosulpiride (SR) 75 mg Capsules)

PAN-L

1. Name of the medicinal product

PAN-L

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Pantoprazole sodium I.P. Equivalent to Pantoprazole 40 mg (as enteric coated)

Levosulpiride 75 mg (as sustained release)

3. Pharmaceutical form

Hard Gelatin Capsule

4. Clinical particulars

4.1 Therapeutic indications

PAN-L is indicated for short term treatment of GERD in adult patients who do not respond to PPI alone.

4.2 Posology and method of administration

One capsule per day in an empty stomach.

4.3 Contraindications

- Known hypersensitivity to pantoprazole, levosulpiride or any of the excipients. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.
- Pheochromocytoma, as it can cause hypertensive attack probably due to release of catecholamine from tumor; such attacks can be controlled with phentolamine.
- Epilepsy.
- In manic conditions and in the manic stages of manic depressive psychoses.
- Concomitant prolactin dependent tumors like pituitary gland prolactinomas and breast cancer.
- Pregnancy and lactation.
- Association with levodopa

4.4 Special warnings and precautions for use

Pantoprazole

Concurrent Gastric Malignancy

Symptomatic response to therapy with Pantoprazole does not preclude the presence of gastric malignancy.

Atrophic Gastritis

Atrophic gastritis has been reported occasionally in gastric corpus biopsies from patients treated long-term with Pantoprazole, particularly in patients who were H. pylori positive.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Cyanocobalamin (Vitamin B-12) Deficiency

Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid- suppressing therapy have

been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are reported.

***Clostridium difficile* associated diarrhea**

Published observational studies suggest that PPI therapy like pantoprazole may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

Several published observational studies reported that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals.

Tumorigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of Pantoprazole. In long-term rodent reported studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Interference with Urine Screen for THC

See Drug Interactions section

Concomitant use of Pantoprazole with Methotrexate

Literature reported that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

USE IN SPECIFIC POPULATIONS

Pediatric Use

The safety and effectiveness of pantoprazoe for short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with GERD have been reported in pediatric patients 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, pantoprazole is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of Pantoprazole for pediatric uses other than EE have not been established.

1 year through 16 years of age

Use of Pantoprazole in pediatric patients 1 year through 16 years of age for short-term treatment (up to eight weeks) of EE associated with GERD is supported by: a) extrapolation of results from adequate and well-controlled studies that supported the approval of Pantoprazole for treatment of EE associated with GERD in adults, and b) safety, effectiveness, and pharmacokinetic studies performed in pediatric patients.

Neonates to less than one year of age

Pantoprazole was not reported to be effective in the randomized, placebo-controlled study in this age group, the use of Pantoprazole for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Geriatric Use

In short-term reported clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with Pantoprazole were similar to those found in patients under the age of 65. The incidence rates of adverse reactions and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

Gender

Erosive esophagitis healing rates in the 221 women treated with Pantoprazole Delayed- Release Tablets in US clinical trials were similar to those found in men. In the 122 women treated long- term with Pantoprazole 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse reactions were also similar for men and women.

Patients with Hepatic Impairment

Doses higher than 40 mg/day have not been studied in patients with hepatic impairment.

Levosulpiride

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in association with other antipsychotic drugs. NMS is associated with hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. In such an event, or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs must be discontinued. The treatment of NMS involves immediate discontinuation of administration of antipsychotic drugs and establishment of intensive symptomatic therapy (particular care should be taken to reduce hyperthermia and correct the dehydration). If resumption of treatment with antipsychotic drugs becomes essential, the patient should be carefully monitored.

Extrapyramidal reactions

Extrapyramidal reactions, mainly akathisia, have been reported with other antipsychotic drugs and for that dosage reduction is warranted.

Gastrointestinal diseases

Levosulpiride should not be used when gastrointestinal stimulation of motility can be harmful, e.g., in presence of gastrointestinal hemorrhage, mechanical obstructions or perforations.

Others

Caution should be exercised in the following patients:

- Patients with convulsion,
- Patients with manic states such as in the manic phase of manic depressive psychosis
- Patients with cardiac insufficiency.
- Patients with cerebrovascular events including risk factors for stroke
- Prolongations of QTc interval or factors that may predispose QTc interval prolongation

(Bradycardia, hypokalemia, congenital QTc prolongation, decreased intracardiac conduction)

- Patients with a history cerebrovascular events (stroke, Venous thromboembolism)
- Consuming other neuroleptics.

USE IN SPECIAL POPULATION

Children

Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

Elderly

The dose should be reduced if there is evidence of renal impairment. Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole

Interference with Antiretroviral Therapy

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

Coumarin Anticoagulants

There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including Pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

Clopidogrel

Concomitant administration of pantoprazole 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 pantoprazole.

Drugs for Which Gastric pH can Affect Bioavailability

Due to its effects on gastric acid secretion, pantoprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, ampicillin esters, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease.

Co-administration of pantoprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving pantoprazole and MMF. Use pantoprazole with caution in transplant patients receiving MMF.

False Positive Urine Tests for THC

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors. An alternative confirmatory method should be considered to verify positive results.

Methotrexate

Concomitant administration of PPIs and methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been reported.

Levosulpiride

Caution is advised when levosulpiride is taken concomitantly with other centrally acting drugs. It can potentiate the cognitive and motor effects of alcohol. CNS depressants including narcotics, analgesics, sedative H_1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives. Lithium increases the risk of extrapyramidal side effects.

Caution is advised with medications that may predispose QTc interval prolongation that include:

- Bradycardia inducing medications: Beta blockers, calcium channel blockers (verapamil, diltiazem), clonidine, and digitalis.
- Medications which induce electrolyte imbalance (particularly hypokalemia), hypokalaemic diuretics, stimulant laxatives, IV amphoterecin B, glucocorticoids, and

etracosectides.

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as pimozide, haloperidol; methadone, imipramine antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine and pentamidine.

Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension.
The effect of levosulpiride on gastrointestinal motility can be antagonized by anticholinergic drugs; narcotics and analgesic drugs.

4.6 Fertility, pregnancy and lactation

Pantoprazole

Pregnancy

Pregnancy Category B: Reproduction studies have been reported in rats at oral doses up to 88 times the recommended human dose and in rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity reported for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

4.7 Effects on ability to drive and use machines

Adverse drug reactions, such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Pantoprazole

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Safety in nine randomized comparative clinical trials in patients with GERD included 1,473 patients on oral PANTOPRAZOLE (20 mg or 40 mg), 299 patients on an H2-receptor antagonist, 46 patients on another proton pump inhibitor, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table.

Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%

Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%			
	Pantoprazole (n = 1,473) %	Comparators (n = 345) %	Placebo (n = 82) %
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7	5.2	9.8

Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for pantoprazole in clinical trials with a frequency of ≤ 2% are listed below by body system:
Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial edema
Gastrointestinal: constipation, dry mouth, hepatitis
Hematologic: leukopenia, thrombocytopenia
Metabolic/Nutritional: elevated CK (creatine kinase), generalized edema, elevated triglycerides, liver enzymes elevated
Musculoskeletal: myalgia Nervous: depression, vertigo Skin and Appendages: urticaria, rash, pruritus Special Senses: blurred vision.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of pantoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
These adverse reactions are listed below by body system:
General Disorders and Administration Conditions: asthenia, fatigue, malaise
Hematologic: pancytopenia, agranulocytosis
Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure
Immune System Disorders: anaphylaxis (including anaphylactic shock) Infections and Infestations: *Clostridium difficile* associated diarrhea Investigations: weight changes
Metabolism and Nutritional Disorders: hyponatremia, hypomagnesemia
Musculoskeletal Disorders: rhabdomyolysis, bone fracture
Nervous: ageusia, dysgeusia
Psychiatric Disorders: hallucination, confusion, insomnia, somnolence
Renal and Urinary Disorders: interstitial nephritis
Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal), and angioedema (Quincke's edema)

Levosulpiride

Cardiovascular disorders:
- Postural hypotension
- QT interval prolongation and ventricular arrhythmias such as torsade de pointes and ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death.

Endocrine disorders:
- Hyperprolactinaemia, reversible effects of levosulpiride on functioning of hypothalamic pituitary gonadal axis.

General disorders and administration site conditions:
- Neuroleptic malignant syndrome
- Weight gain

Hepatobiliary disorders:
- Increase in hepatic enzymes

Nervous system disorders:
- Sedation or drowsiness. Insomnia has been reported.

- Extrapyramidal symptoms and related disorders
- Parkinsonism and related symptoms: tremor, hypertonia, hypokinesia, hypersalivation
- Acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus),

Akathisia:

These symptoms are generally reversible upon administration of antiparkinsonian medication.

- Tardive dyskinesia (characterised by rhythmic, involuntary movements primarily of the tongue and/or the face) have been reported, as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
- Convulsions have been reported, in particular in patients with epilepsy.

Reproductive system and breast disorders:

- Disorders related to hyperprolactinaemia
- Galactorrhoea
- Amenorrhoea
- Gynaecomastia
- Breast enlargement and breast pain
- Orgasmic dysfunction, erectile dysfunction, change in libido

Skin and subcutaneous tissue disorders:

- Maculo-papular rash

Vascular disorders:

- Venous thromboembolism, pulmonary embolism and deep vein thrombosis have been reported with antipsychotic drugs-frequency unknown

4.9 Overdose

Pantoprazole

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of pantoprazole.

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

Levosulpiride

The clinical manifestation of poisoning depends on amount of dose ingested. Symptoms like, restlessness, clouding of consciousness, extrapyramidal symptoms, agitation, confusion, hypotension, rarely coma at higher dose are reported. It is partly removed by hemodialysis. There is no specific antidote topoisoning of levosulpiride, only supportive measures should be undertaken and close monitoring of cardiac functions and vitals is recommended. Overdosage should be treated with alkaline diuresis, antiparkinsonian drugs, if necessary, andanticholinergic in case of severe extrapyramidal symptoms.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pantoprazole

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the H^+/K^+-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. It has been reported that the binding to the H^+/K^+-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Levosulpiride

Levosulpiride is selective blocks D_2 receptors at the submucosal and myenteric plexus peripheral level. Significant amounts of dopamine are present in the gastrointestinal tract, where it causes a marked inhibitory effect on motility. Dopamine acting at inhibitory dopamine D_2 receptors located on excitatory neuronal structures and smooth muscle was found to cause reduction in lower oesophageal sphincter tone, gastric tone and intragastric pressure, as well as inhibition of gastro duodenal co-ordination. Blockade of peripheral D_2 receptors is considered the main mechanism by which antidopaminergic prokinetic drugs, such as levosulpiride, exert their gastrointestinal stimulatory effect. Antidopaminergic properties of levosulpiride at D_2 receptors of the chemoreceptor trigger zone in the area postrema of the fourth ventricle floor is responsible for anti-emetic property.

5.2 Pharmacokinetic properties

Absorption:

Pantoprazole

After administration of a single or multiple oral 40 mg doses of Pantoprazole Tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and Cmax was 2.5 µg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of Pantoprazole Tablets with food may delay its absorption up to 2 hours or longer; however, the Cmax and the extent of pantoprazole absorption (AUC) are not altered. Thus, Pantoprazole Tablets may be taken without regard to timing of meals.

Levosulpiride

The bioavailability of levosulpiride, when given orally is low (about 27% to 34%) with incomplete absorption as opposed to presystemic metabolism. Food reduces absorption by 30%. The time to peak concentration is 3 to 9 hours with median t_{max} 5.5 hours. The oral AUC values for levosulpiride extended release tablet for a dose of 200 mg is 6050 ng.hr/ml.

Distribution:

Pantoprazole

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Levosulpiride

Levosulpiride displays a protein binding of about 14% and a volume of distribution of 1 to 2.7 L/kg which is similar in elderly and younger subjects.

Metabolism:

Pantoprazole

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Levosulpiride

Metabolism does not occur and the drug is excreted unchanged into the urine. The renal clearance is 15 to 30%. The drug is substantially excreted in the feces due to poor absorption. The lack of hepatic metabolism makes metabolic interactions with cytochrome P-450 related substrates very unlikely.

Excretion:

Pantoprazole

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Levosulpiride

The elimination half-life ranges from 4.7 to 14.6 hours for oral 200mg dose of levosulpiride ER tablet. The elimination half-life is prolonged in patients with renal impairment.The peak concentrations, time to peak levels and the elimination half-life is similar in younger and elderly patients.

6. Pharmaceutical particulars

6.1 Shelf life

18 months

6.2 Special precautions for storage

Store at room temperature. Protect from light and moisture.

6.3 Nature and contents of container

Pack of 10's

7. Marketed By

ALKEM

Alkem Laboratories Ltd.
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