Summary of Product Characteristics (SmPC)

1.0 Name of the medicinal product: SULPANTO

2.0 Qualitative and quantitative composition

Each Hard Gelatin capsule contains:
Pantoprazole BP…….....40 mg
(as enteric coated pellets)
Levosulpiride BP…....….75 mg
(as sustained release pellets)
Excipients Q.S.
Approved colors used in Pellets and Capsule shells.

3.0 Pharmaceutical form

Oral Solid Dosage Form

4.0 Clinical particulars

4.1 Therapeutic indications

Sulpanto is indicated in:

LEVOSULPIRIDE+PANTOPRAZOLE belongs to a group of medicines called gastrointestinal agents used to treat gastro-oesophageal reflux disease (GERD), acidity, indigestion, heartburn, and peptic ulcers

4.2 Posology and method of administration

The recommended dosage of SULAPNTO Capsules is one capsule once daily before meals. Capsules should be swallowed whole and are not to be chewed.

4.3 Contraindications

Hypersensitivity to pantoprazole, levosulpiride or any other components in the formulation

- Pheochromocytoma – as it can cause a hypertensive attack, probably due to release of catecholamine from a tumor; such attacks can be controlled with phentolamine
- Epilepsy, manic states such as in the manic phase of manic-depressive psychosis.
- Concomitant prolactin-dependent tumors such as pituitary gland prolactinomas and breast cancer
- Pregnancy and lactation
- Severe renal and hepatic insufficiency
- Levosulpiride is contraindicated in gastrointestinal bleeding and intestinal obstruction

4.4 Special warnings and precautions for use

Pantoprazole

Presence of Gastric Malignancy

Symptomatic response to therapy with pantoprazole sodium does not preclude the presence of gastric malignancy. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

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

Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was sub-acute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. SLE is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug-induced SLE. Onset of SLE typically occurred within days to years after initiating treatment, primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopaenia were also reported. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving pantoprazole sodium delayed-release tablets, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4–12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Cyanocobalamin (Vitamin B12) 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 B12) 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 observed.

Clostridium difficile-associated Diarrhoea
Published observational studies suggest that PPI therapy such as pantoprazole sodium may be associated with an increased risk of Clostridium difficile-associated diarrhoea, 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 PPI therapy appropriate to the condition being treated.

Bone Fracture
Several published observational studies suggest that 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 of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias and seizures. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

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

Fundic Gland Polyps PPI
use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond 1 year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Interference with Investigations for Neuroendocrine Tumours
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false-positive results in diagnostic investigations for neuroendocrine tumours. Healthcare providers should temporarily stop pantoprazole sodium delayed-release tablet treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Interference with Urine Screen
THC There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole sodium delayed-release tablets.

Concomitant Use of Pantoprazole
Methotrexate Literature suggests 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.

Hepatic Impairment
In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole sodium, particularly on long-term use. In the case of a rise of the liver enzymes, the treatment should be discontinued.

Combination Therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

HIV Protease Inhibtiors
Co-administration of pantoprazole sodium is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability. If the combination of HIV protease inhibitors with a PPI is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole sodium dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitors may need to be adjusted.

Long-term Treatment
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal Infections Caused by Bacteria
Pantoprazole sodium, like all PPIs, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole sodium may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile.

Levosulpiride
Patients may experience drowsiness, dizziness and dyskinesia with the use of levosulpiride and, hence, patients under treatment should be advised to avoid driving vehicles or operating machinery. Levosulpiride should not be used when stimulation of gastrointestinal motility could be harmful, e.g. in the presence of gastrointestinal bleeding, mechanical obstruction or perforation. Cautious use is advised in patients with cardiovascular disease or a family history of QT prolongation and in patients with risk factors for stroke. During treatment with antipsychotic drugs, potentially fatal complex symptoms called neuroleptic malignant syndrome (NMS) have been reported. Avoid concomitant therapy with other neuroleptics.

4.5 Interaction with other medicinal products and other forms of interaction

Pantoprazole
Pantoprazole sodium is extensively metabolised in the liver via the cytochrome (CY) P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.
Interaction studies with drugs also metabolised with these pathways such as carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyloestradiol did not reveal clinically significant interactions.
An interaction of pantoprazole sodium with other medicinal products or compounds, which are metabolised using the same enzyme system, cannot be excluded. Results from a range of interaction studies demonstrate that pantoprazole sodium does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with Pglycoprotein related absorption of digoxin.

Antacids
There were no interactions with concomitantly administered antacids.

HIV Protease Inhibitors
Co-administration of pantoprazole sodium is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir, due to significant reduction in their bioavailability. If the combination of HIV protease inhibitors with a PPI is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole sodium dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitors may need to be adjusted.

Coumarin Anticoagulants (Phenprocoumon or Warfarin)
Co-administration of pantoprazole sodium with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole sodium and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Clopidogrel
Concomitant administration of pantoprazole sodium 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 sodium.

Drugs for Which Gastric pH Can Affect Bioavailability
Pantoprazole sodium causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole sodium may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole, ampicillin esters, iron salts and other medicines such as erlotinib).

False-Positive Urine Tests for THC
There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

Methotrexate
Case reports, published population pharmacokinetic studies and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high doses; see methotrexate prescribing information) 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 conducted.

4.6 Pregnancy and lactation

Pregnancy Category B – Pantoprazole
There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of foetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactating Women
Pantoprazole sodium and its metabolites are excreted in the milk of rats. Pantoprazole sodium 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. Based on the potential for tumourigenicity shown for pantoprazole sodium 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

Pregnant Women

Pregnancy Category B-Levosulpiride

Sustained-release levosulpiride capsules are contraindicated during pregnancy.

Lactating Women Sustained-release levosulpiride capsules are contraindicated during lactation.

Paediatric Patients Safety and efficacy of levosulpride has not been established in paediatric patients.

4.7 Effects on ability to drive and use machines

Pantoprazole sodium has no or negligible influence on the 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
Levosulpiride may have an influence on the ability to drive and use machines

4.8 Undesirable effects

Pantoprazole
The following serious adverse reactions are described below and elsewhere in the labelling:
● Acute Interstitial Nephritis
● Clostridium difficile-associated Diarrhoea
● Bone Fracture
● Cutaneous and Systemic Lupus Erythematosus Cyanocobalamin (Vitamin B12) Deficiency
● Hypomagnesaemia Fundic Gland Polyps
● Acute Kidney Injury

Adverse effects reported with **levosulpiride** include drowsiness, amenorrhoea, gynecomastia, galactorrhoea, and change in libido.
Serious side effects include neuroleptic malignant syndrome and drug-induced movement disorders.

4.9 Overdose

Pantoprazole
Experience in patients taking very high doses of pantoprazole sodium (>240 mg) is limited. Spontaneous postmarketing reports of overdose are generally within the known safety profile of pantoprazole sodium. Pantoprazole sodium is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive. Single oral doses of pantoprazole sodium 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
In the normal therapeutic dose range, the possibility of side effects is less. But extrapyramidal disturbances and sleep disorders may occur with higher doses and in patients who are sensitive to dopamine antagonists. In such cases, therapy should be stopped, or the dose should be reduced as dictated by the clinical condition of the patient

5.0 Shelf life: 36 Months

6. Pharmaceutical particulars

6.1 List of excipients

Red/clear transparent Empty Hard gelatin capsule shells. Size `2',