Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Sulpanto Capsules

2. Qualitative and quantitative composition
Each hard gelatin capsule contains: Pantoprazole 40mg (as enteric coated pellets) and Levosulpiride 75mg (as sustained release pellets)

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Red/clear transparent size "2" hard gelatin capsule containing white colour pellets.

4. Clinical particulars

4.1 Therapeutic indications
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 followup 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 PPIinduced 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 longterm 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 Fertility, 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 most commonly reported adverse drug reactions, during controlled clinical trials with pantoprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as:
very common (≥1/10),
common (≥1/100 to <1/10),
uncommon (≥1/1,000 to <1/100),
rare (≥1/10,000 to <1/1,000),
very rare (<1/10,000),
not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Infection				
Blood and lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity[1,2]		
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia 4
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic gland polyps (benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis

Hepatobiliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		
Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip,wrist or spine			
Renal and urinary disorders		Urinary tract infection	Interstitial nephritis		
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

1 Includes facial swelling, hypotension and dyspnea

2 Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

3 Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Pantoprazole is first initiated in such

patients

[4] See Special warnings and precautions for use

Proton pump inhibitor use was found to be associated with increased risks for acute kidney injury and chronic kidney disease.

Levosulpiride

The following side effects can occur with the use of this drug;

- Acute muscular dystonia characterized by abnormal movements (twitching, tremor etc.) of hands, leg, tongue and facial muscles.
- Sedation or drowsiness (because of decrease in sensory inputs to reticular activating system)
- Increase in plasma prolactin levels manifested by breast enlargement, production of milk and stopping of menstrual periods. This can be taken care of with the use of lower dose of this drug.
- Neuroleptic malignant syndrome (characterized by hyperpyrexia, muscle rigidity, increased myoglobin and creatine kinase; the last two suggestive of muscle damage.
- Akathisia (uncontrollable desire to move about without any anxiety).
- Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of face, mouth and jaw. The reason for tardive dyskinesia is synthesis of newer DA receptors which are supersensitive to even a small amount of DA. This causes a decrease in cholinergic activity in the striatum followed by decrease in GABA release. This decreased in inhibitory GABA is responsible for increased involuntary motor activity.
- Postural hypotension (because of autonomic blockade), tolerance develops to this effect after some time.
- Weight gain.
- Elevated liver transaminases.

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. Pharmacological properties

5.1 Pharmacodynamic properties

Pantoprazole

Anti-secretory activity: After oral administration of a 20 mg dose of pantoprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of pantoprazole sodium are 69 % and 82 % respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of pantoprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Decreased gastric acidity due to any means, including proton pump inhibitors such as pantoprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Serum gastrin effects: In clinical studies patients were treated once daily with 40mg pantoprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to

reference range.

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Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving pantoprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection. In over 250 patients followed for 36 months of continuous therapy, no significant change in findings present at baseline was observed.

Other effects: Systemic effects of pantoprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Pantoprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.

Studies in healthy subjects have shown that pantoprazole sodium does not have clinically significant interactions with amoxicillin. Pantoprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H. pylori* infection.

Levosulpiride

Like its parent compound, levosulpiride shows antagonism at D3 and D2 receptors present presynaptically as well as postsynaptically in the rat striatum or nucleus accumbens. The preferential binding of the presynaptic dopamine receptors decreases the synthesis and release of dopamine at low doses

whereas it causes postsynaptic D2 receptor antagonism at higher dose. This receptor profile of the drug along with its limbic selectivity explains its effectiveness in the management of both positive and negative symptoms of schizophrenia.

5.2 Pharmacokinetic properties

Rabeprazole

Pantoprazole 40 mg is an enteric-coated pellet formulation of pantoprazole sodium. This presentation is necessary because pantoprazole is acid-labile. Absorption of pantoprazole therefore begins only after the pellet leaves the stomach. Absorption is rapid, with peak plasma levels of pantoprazole occurring approximately 3.5 hours after a 40 mg dose. Peak plasma concentrations (C_{max}) of pantoprazole and AUC are linear over the dose range of 20 mg to 40 mg. Absolute bioavailability of an oral 40 mg dose (compared to intravenous administration) is about 52 % due in large part to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of pantoprazole sodium.

Pantoprazole is approximately 97 % bound to human plasma proteins.

Pantoprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that pantoprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations pantoprazole neither induces nor inhibits CYP3A4; and although *in vitro* studies may not always be predictive of *in vivo* status these findings indicate that no interaction is expected between pantoprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

Following a single 40 mg ^{14}C labelled oral dose of pantoprazole sodium, no unchanged drug was excreted in the urine. Approximately 90 % of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces. Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 40 mg dose of rabeprazole.

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5 ml/min/1.73 m^2), the disposition of pantoprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35 % lower than the corresponding parameters in healthy volunteers. The mean half-life of pantoprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.

Following a single 40 mg dose of pantoprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3-fold increase in half-life of pantoprazole compared to the healthy volunteers. However, following a 40 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of pantoprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Elimination of pantoprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 40 mg of pantoprazole sodium, the AUC approximately doubled, the C_{max} increased by 60 % and t½ increased by approximately 30 % as compared to young healthy volunteers. However, there was no evidence of pantoprazole accumulation.

Following a 40 mg daily dose of pantoprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolizers whilst C_{max} had increased by only 40 %.

Levosulpiride

The parent drug is given in a dose of 400-1800 mg orally daily although a much lower dose is effective for producing antidepressant effect (about 50-300 mg). The plasma t1/2 of the drug is about 6-8 hours. The drug is chiefly excreted through the renal route.

5.3 Preclinical safety data

Animal Toxicology or Pharmacology

Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but *in vivo* micronucleus and *in vivo* and *in vitro* DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6. Pharmaceutical particulars

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage:

Store below 30℃

6.5 Nature and contents of container

10 Capsules packed in Alu Alu blister Pack, such 3 blister is packed in a carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Manufacturing site address:

Company name: Aksharam Pharma Pvt. Ltd.
Address: Plot No,1&2, Akshar Ind, Estate, Rajkot Highway Road, Opp. Tri-Mandir, Kherali, Dist. Surendranagar (363020), Gujarat, India
Country: India

Local Technical Representative:

Company name: SIMBA PHARMACEUTICALS LTD.
Address: 1 st Floor, Almont Park, Westlands .
P.O. Box 1541-00606 Nairobi
Country: KENYA

8. Marketing authorization number
CTD10483

9. Date of first registration
03/08/2023

10. Date of revision of the text
15/09/2023

11. Dosimetry
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals
Not Applicable