Summary of Product Characteristics

1. Name of the medicinal Product
Pantoprazole for Injection BP 40 mg

2. Qualitative and Quantitative Composition
Qualitative declaration
Pantoprazole Sodium (Sterile and Lyophilized)

Quantitative declaration
Pantoprazole Sodium (Sterile and Lyophilized) Eq. to Pantoprazole 40 mg

3. **Pharmaceutical Form**
Dry Powder for Injection
White to off-white powder.

4. Clinical Particulars
1. Therapeutic Indications
PENTALINK-40 is used for the treatment of Reflux oesophagitis, gastric and duodenal ulcer, zollinger-ellison-syndrome and other pathological hypersecretory conditions.

2. Posology and Method of Administration
Method of administration:
Pentalink-40 Powder for Solution for Injection should be administered (I.V) intravenously only.

Intravenous administration of Pentalink-40 Powder for Solution for Injection is recommended only if oral administration is not appropriate.

It should be use on intravenous for up to 7 days. Therefore, as soon as oral therapy is possible, treatment with Pentalink-40 Powder for Solution for Injection IV should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Dosage:
Gastric and duodenal ulcer, reflux oesophagitis: The recommended intravenous dose is one vial of Pentalink-40 Powder for Solution for Injection (40 mg pantoprazole) per day.

Zollinger-Ellison Syndrome and other pathological hypersecretory conditions: For the long-term management of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions treatment should start with a daily dose of 80 mg of pantoprazole I.V. Afterward, the dosage can be titrated up or down as directed by physician. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. In case a rapid acid control is required, a starting dose of 2 x 80 mg Pentalink-40 Powder for Solution for Injection is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within one hour in the majority of patients.

Hepatic impairment: A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment.

Renal impairment: No dose adjustment is necessary in patients with impaired renal function.
Elderly: No dose adjustment is necessary in elderly patients.

Pediatric patients: A Very Inadequate of safety and efficacy established data in below 18 years of age children. Therefore, it should not recommend for use in patients below 18 years of age.

Instructions for reconstitution preparation: A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%w/v) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a colourless to faintly yellow solution.

The prepared solution must be administered directly IV or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9% w/v) solution for injection.

· Glass or plastic containers should be used for dilution.

· After preparation the solution must be used within 12 hours. It should be administered intravenously over 2-15 minutes.

· Although from a microbiological point of view, the prepared solution for injection should be used immediately.

· Pentalink-40 Powder for Solution for Injection should not be prepared or mixed with solvents other than specified. The contents of the vial are for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) It should not be used and disposed it in accordance with local requirements.

3. Contraindications
Hypersensitivity to the pantoprazole or substituted benzimidazoles, or to any of the excipients.

4.4 Special Warnings and Special Precautions for Use
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.

Hepatic impairment: In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be stopped.

Co-administration with HIV protease inhibitors: Co-administration of atazanavir with proton pump inhibitors is not recommended.

Gastrointestinal infections caused by bacteria: Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile.

Hypomagnesaemia: Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole 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 arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), physician should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures: Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the overall risk of fracture by 10–40% (hip, wrist and spine fracture) predominantly in the elderly or in presence of other recognized 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.
Subacute cutaneous lupus erythematosus (SCLE): Proton pump inhibitors 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 pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels

have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Pregnancy: Pantoprazole 40 mg should not be used during pregnancy unless clearly necessary.

Lactation: Distributed into milk. Discontinue nursing or the drug because of potential risk in nursing infants.

Pediatric Use: Safety and efficacy not established in children <18 years of age.

5. Interaction with other medicinal products and other forms of interaction

Medicinal products with pH dependent absorption pharmacokinetics: e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibitors: Co-administration of pantoprazole 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 inhibtiors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants: It did not affect the pharmacokinetics of warfarin, phenoprocoumon. However, there may reports of increased INR and prothrombin time and it may lead to abnormal bleeding, or serious effect. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate: Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors reported to increase methotrexate levels in some patients. Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions: Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4. Interaction studies with medicinal products also metabolized with these pathways, i.e. carbamazepine, diazepam, glibenclamide, nifedipine, CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac,naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions. There were no interactions with concomitantly administered antacids and antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions found.

6. Pregnancy and Lactation

Pregnancy: Pantoprazole 40 mg should not be used during pregnancy unless clearly necessary.

Lactation: Distributed into milk. Discontinue nursing or the drug because of potential risk in nursing infants.

7. Effects on ability To Drive and use Machines

Not Applicable

8. Undesirable Effects

The most commonly adverse effect is injection site thrombophlebitis. Diarrhoea and headache, occurred in patients. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders: Rare: Agranulocytosis, Very rare: Thrombocytopenia;

Leukopenia, Pancytopenia. Immune system disorders: Rare: Hypersensitivity (including Anaphylactic, reactions and Anaphylactic shock).

Metabolism and nutrition disorders: Rare: Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes.

Psychiatric disorders: Uncommon: Sleep disorders, Rare: Depression and Very rare: Disorientation (and all aggravations), Not known: Hallucination; Confusion (especially in predisposed patients, as well as the aggravation of these symptoms in Case of preexistence). Nervous system disorders: Uncommon: Headache Dizziness, Rare: Taste disorders, Not known: Paraesthesia.

Eye disorders: Rare: Disturbances in vision / blurred vision.

Gastrointestinal disorders: Common: Fundic gland polyps (benign), Uncommon: Diarrhoea. Nausea / vomiting; abdominal distension and bloating; Constipation; Dry mouth; abdominal pain and discomfort, Not known: Microscopic colitis.

Hepatobiliary disorders: Uncommon: Liver enzymes increased (transaminases, γ-GT), Rare: Bilirubin increased, Not known: Hepatocellular injury; Jaundice; Hepatocellular failure.

Skin and subcutaneous tissue disorders: Uncommon: Rash / exanthema / eruption; Pruritus Rare: Urticaria, Angioedema, Not known: Stevens-Johnson syndrome, Lyell syndrome, Erythema multiforme; Photosensitivity; Sub acute cutaneous lupus erythematosus Musculoskeletal and connective tissue disorders: Uncommon: Fracture of the hip, wrist or spine Rare: Arthralgia; Myalgia, Not known: Muscle spasm as a consequence of electrolyte disturbances.

Renal and urinary Disorders: Not known: Interstitial nephritis (with possible progression to renal failure).

Reproductive system and breast disorders: Rare: Gynaecomastia.
General disorders and administration site conditions: Common: Injection site thrombophlebitis, Uncommon: Asthenia, fatigue and malaise. Rare: Body temperature increased; Oedema peripheral.

9. Overdose
There are no known symptoms of overdose in man. Systemic exposure with up to 240 mg administered intravenously over two minutes were well tolerated. Pantoprazole is extensively protein bound, it is not readily dialysable. In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. Pharmacological Properties

1. Pharmacodynamics Properties
Pantoprazole is a substituted benzimidazole, which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+/K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dosedependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within two weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin).

2. Pharmacokinetic Properties
General Pharmacokinetics: Pharmacokinetics is not varying after single or repeated administration. In the dose range of 10 to 80 mg the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Distribution: The serum protein binding is about 98 %. Volume of distribution is about 0.15 lit/kg.

Metabolism: The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4.

Excretion: Terminal half-life is about 1 hour and clearance is about 0.1 lit/h/kg. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination, half-life does not correlate with the much longer duration of action (inhibition of acid secretion). Renal elimination represents the major route of excretion (about 80 %) for the metabolites of Pantoprazole; the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethyl pantoprazole, which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of Pantoprazole.

Special populations:
Poor metabolisers: Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals, the metabolism of pantoprazole probably mainly catalyzed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These outcomes have no implications for the posology of pantoprazole.

Renal impairment: No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (incl. dialysis patients). It has short half-life. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment: Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum concentration only increased slightly.

Elderly: A slight increase in AUC and Cmax in elderly compared with younger counterparts is also not clinically relevant.

Paediatric population: Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2-16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

3. Preclinical Safety Data
Not Applicable

6. Pharmaceutical Particulars
1. List of Excipients
None

2. Incompatibilities
Not applicable

3. Shelf Life
24 months
The product should be used immediately after reconstitution.

4. Special Precautions for Storage
Do not store above 30°C. Protect from light & moisture.

5. Nature and Contents of Container
White to off-white powder is filled in 10 ml USP-I amber glass vial with 20 mm grey butyl RFU sterile rubber stopper & 20 mm red flip off seal. Such 1 labeled vial is packed in Printed Carton with Packing Insert.

6. Special precaution for disposal and other handling
No special requirements for disposal.

7. Marketing Authorization Holder And Manufacturing Site Addresses

Name and Address of Marketing Authorization Holder
Lincoln Pharmaceuticals Limited
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8. **Marketing Authorization Number**
TAN 22 HM 0133

9. **Date of First <Registration> / Renewal of The <Registration>**
13/04/2022

10.**Date of Revision of the Text**