Bosch

For Healthcare Professional only

Zentro™ 40mg Injection

(Pantoprazole)

IV Infusion/Injection

زینٹرو انفیوژن/انجکشن ۴۰ ملی گرام

(پینٹوپرازول)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
Pantoprazole....40mg
as Pantoprazole Sodium USP (Sesquihydrate)
(Product Specs.: BP)

PHARMACEUTICAL FORM
Powder for solution for Infusion / Injection

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:
Zentro Injection is indicated for the treatment of the following.
- Reflux esophagitis
- Gastric and duodenal ulcer
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Zentro Injection is recommended for up to 7 days only if oral administration is not appropriate.

Gastric and duodenal ulcer, reflux esophagitis
The recommended intravenous dose is one vial of Zentro 40 mg per day.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg. Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg 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 is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special populations

Pediatric population
The safety and efficacy in children aged under 18 years have not been established. Therefore, it is not recommended for use in patients below 18 years of age.

Hepatic Impairment
A daily dose of 20 mg (half a vial of 40 mg) 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.

Method of administration
A ready-to-use solution is prepared in 10 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection. The prepared solution may be administered directly or may be administered after mixing it with 100 mL sodium chloride 9 mg/mL (0.9 %) solution for injection or glucose 55 mg/mL (5%) solution for injection. After preparation the solution must be used within 12 hours. The medicinal product should be administered intravenously over 2 - 15 minutes.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or substituted benzimidazoles.

Special warnings and precautions for use
Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anemia or melena) and when gastric ulcer is suspected or present, malignancy should be excluded. Further investigation is to be considered if symptoms persist despite adequate treatment.

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 discontinued.

Co-administration with HIV protease inhibitors
Co-administration 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.

Gastrointestinal infections caused by bacteria
Treatment may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile.

Hypomagnesemia
Severe hypomagnesemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. In most affected patients, hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) 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 hypomagnesemia (e.g., diuretics), should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)
PPIs are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Bone fractures
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of 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 and should have an adequate intake of vitamin D and calcium.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. To avoid this interference, 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.

Interaction with other medicinal products and other forms of interaction
Medicinal products with pH dependent absorption pharmacokinetics
Because of profound and long-lasting inhibition of gastric acid secretion, it may interfere with the absorption of medicinal products where gastric pH is an important determinant of oral bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

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

Medicinal products that inhibit or induce CYP2C19:
Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

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.
There are no interactions with concomitantly administered antacids.

Fertility, pregnancy, and lactation
Safety during pregnancy and lactation has not been established

Pregnancy: As a precautionary measure, it is preferable to avoid the use of Pantoprazole during pregnancy.
Lactation: It is excreted in breast milk therapy should be taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

Fertility: There is no evidence of impaired fertility following the administration.

Effects on ability to drive and use machines
It 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.

Undesirable effects
Adverse reactions identified from frequency of the following convention: 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.

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Thrombocytopenia; Leukopenia; Pancytopenia	Very rare
	Agranulocytosis	Rare
Immune system disorders	Hypersensitivity (including anaphylactic reactions and anaphylactic shock)	Rare
Psychiatric disorders	Sleep disorders	Uncommon
	Depression (and all aggravations)	Rare
	Disorientation (and all aggravations)	Very rare
	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)	Not known
Nervous system disorders	Headache, Dizziness	Uncommon
	Taste disorders	Rare
	Paresthesia	Not known
Eye disorders	Disturbances in vision/ blurred vision	Rare
Gastrointestinal disorders	Fundic gland polyps (benign)	Common
	Diarrhea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort	Uncommon
	Microscopic colitis	Not known
Hepatobiliary disorders	Liver enzymes increased (transaminases, γ-GT)	Uncommon
	Bilirubin increased	Rare
	Hepatocellular injury; Jaundice; Hepatocellular failure	Not known
Skin and subcutaneous tissue disorders	Rash / exanthema / eruption; Pruritus	Uncommon
	Urticaria; Angioedema	Rare
	Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus, Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Musculo-skeletal and connective tissue disorders	Fracture of the hip, wrist or spine	Uncommon
	Arthralgia; Myalgia	Rare
	Muscle spasm	Not known
Renal and urinary disorders	Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)	Not known
Reproductive system and breast disorders	Gynecomastia	Rare
General disorders	Injection site thrombophlebitis	Common
	Asthenia, fatigue and malaise	Uncommon
	Body temperature increased; Oedema peripheral	Rare

OVERDOSE
In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of gastric acid by specific blockade of the proton pumps of the parietal cells.
It 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 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment 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). The effect is the same whether the product is given orally or intravenously.

Pharmacodynamic effects
Pantoprazole increases gastrin values in fasting patients. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in very rare cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia).
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 tumors.

PHARMACOKINETIC PROPERTIES
General Pharmacokinetics
Pharmacokinetics do not vary 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
Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

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

Elimination
Terminal half-life is about 1 hour and clearance is about 0.1 l/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 are excreted with the feces. The main metabolite in both the serum and urine is desmethylpantoprazole 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 metabolizers: After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve is approximately 6 times higher in poor metabolizers than having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations increased by about 60 %.

Renal impairment: No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (incl. dialysis patients). As pantoprazole's half-life is short, 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 time 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 by a factor of 1.5 compared with healthy subjects.

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

Pediatric population: Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there is no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution are in accordance with adults.

PHARMACEUTICAL PARTICULARS
Incompatibilities
This medicinal product must not be mixed with other medicinal products

Shelf life
2 years

Special precautions for storage
Protect from heat, sunlight & moisture, store at room temperature 15°C - 30°C.
The expiration date refers to the product correctly stored at the required condition.
Keep out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION
Zentro (Pantoprazole) 40mg injection is available as one vial per pack with 2x5ml ampoules of Soride (Sterile Sodium Chloride) 0.9% as solvent.

MARKETING AUTHORISATION HOLDER
Head Office:
Bosch Pharmaceuticals (Pvt.) Ltd.,
8, Modern Society, Tipu Sultan Road,
Karachi-75350 (Pakistan).

Manufacturing Site:
Bosch Pharmaceuticals (Pvt.) Ltd.,
Plot No. 209, Sector 23, Korangi Industrial area, Karachi-Pakistan.

MARKETING AUTHORISATION NUMBER(S)
045388

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12-06-2007 / 11-06-2022

DATE OF REVISION OF THE TEXT
18-12-2023

ہدایات:- صرف بڑوں کے لئے :
محلول بنانے کے لئے ساتھ دیئے گئے سالوینٹ کو وائل میں حل کریں۔
دھوپ، گرمی اور نمی سے محفوظ ۱۵ - ۳۰ ڈگری سینٹی گریڈ درجۂ حرارت پر رکھیں۔
بچّوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
209, Sector 23, Korangi Industrial Area,
Karachi - Pakistan.
For **Bosch Pharmaceuticals (Pvt.) Ltd.**
221-223, Sector 23, K.I.A. Karachi-Pakistan.

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(Pantoprazole)

IV Infusion/Injection

زینٹرو انفیوژن/انجکشن ۴۰ ملی گرام

(پینٹوپرازول)

FIRST & ONLY CERTIFIED HALAAL

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PHARMACEUTICAL COMPANY