APPROVED
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Health of Ukraine
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INSTRUCTION
for medical use

ZOLOPANT®

Composition:
active substance: pantoprazole;
1 tablet contains pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg;
excipients: sodium carbonate anhydrous, mannitol (E 421), crospovidone, hydroxypropylcellulose, calcium stearate, methacrylate copolymer dispersion, triethyl citrate, sodium lauryl sulphate, titanium dioxide (E 171), iron oxide yellow (E 172), talc, Opadry 03F58750 white*.
* Opadry 03F58750 white: hypromellose, titanium dioxide (E 171), polyethylene glycol, talc.

Pharmaceutical form. Enteric coated tablets.
Basic physical and chemical properties: yellow oval biconvex film-coated tablets.

Pharmacotherapeutic group.
Drugs for acid-related disorders. Proton pump inhibitor**.**
ATC Code A02B C02.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
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 dose-dependent and affects both basal and stimulated acid secretion. In most patients, the symptoms disappear within 2 weeks. The use of pantoprazole, as well as other proton pump inhibitors (PPI) and H_2-receptor inhibitors, reduces acidity in the stomach and thereby increases gastrin secretion in proportion to the reduction in acidity. The increase in gastrin secretion 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 active substance is given orally or intravenously.
The fasting gastrin values increase under pantoprazole. Upon short-term use, in most cases gastrin levels 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 isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is sometimes observed during long-term treatment (similar to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of progenitor cells of neuroendocrine tumors (atypical hyperplasia) or gastric neuroendocrine tumors as were found in animal studies, has not been observed in humans. Given the results of animal studies, we cannot completely exclude the impact of long-term (over one year) pantoprazole treatment on endocrine parameters of the thyroid gland. During

treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Moreover, the level of chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may affect the results of studies for neuroendocrine tumors. Available published evidence suggests that PPI 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 the reference range.

Pharmacokinetics.

Absorption.

Pantoprazole is rapidly absorbed, and maximum plasma concentrations are achieved even after a single oral dose of 20 mg. On average at about 2–2.5 hours after administration the maximum serum concentrations (C_{max}) of about 1–1.5 μg/ml are achieved; the concentration remains constant after multiple administrations. Pharmacokinetic properties do not change after single or repeated administration. Within the dose range from 10 to 80 mg, the plasma pharmacokinetics of pantoprazole remains linear both after oral and intravenous administration. It has been found that the absolute bioavailability of the tablets is about 77 %. Concomitant intake of food has no influence on the area under the curve "plasma concentration–time" (AUC) or C_{max}, and therefore bioavailability. Only the variability of the latent period is increased by concomitant food intake.

Distribution.

Pantoprazole's serum protein binding is about 98 %. The 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 includes oxidation by CYP3A4.

Elimination. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. A few cases of delayed elimination have been registered. Due to the specific binding of pantoprazole to the proton pumps of the parietal cells the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

The major part of metabolites of pantoprazole is excreted with the urine (about 80 %), the rest is 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 patient groups.

Poor metabolizers. About 3 % of the European population have reduced functional activity of the CYP2C19 enzyme; they are called poor metabolizers. In these individuals, the metabolism of pantoprazole is probably mainly catalyzed by the CYP3A4 enzyme. After a single-dose administration of 40 mg pantoprazole, the AUC was approximately 6 times higher in poor metabolizers than in subjects having a functionally active CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Impaired renal function. No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, 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 hours), excretion is still rapid and thus accumulation does not occur.

Impaired hepatic function. Although for patients with liver cirrhosis (classes A and B according to the Child-Pugh score) the half-life values are increased to 3–6 hours, and the AUC is increased 3–5-fold, the C_{max} only increases slightly by a factor of 1.3 compared with healthy subjects.

Elderly patients. An insignificant increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Children.

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 to 16 years the AUC and C_{max} were in the range of corresponding values in adults.

Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 to 16 years there was no significant association between pantoprazole clearance and the patient's age or bodyweight. The AUC and volume of distribution were in accordance with data from adults.

Clinical characteristics.

***Indications*.**

Adults and children 12 years of age and above.

Symptomatic treatment of gastroesophageal reflux disease.

Prolonged treatment and prevention of relapse of reflux esophagitis.

Adults.

Prevention of gastric and duodenal ulcers caused by taking non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at risk who require prolonged use of NSAIDs.

Contraindications.

Hypersensitivity to the active substance or to any other drug components, to benzimidazole derivatives.

Interaction with other medicinal products and other forms of interaction.

Medicinal products with pH-dependent absorption. Because of profound and long-lasting inhibition of hydrochloric acid secretion, pantoprazole may interfere with the absorption of medicinal products where gastric pH is an important determinant of their availability (e.g. some antifungals such as ketoconazole, itraconazole, posaconazole or other preparations such as erlotinib).

HIV-protease inhibitors. Co-administration of pantoprazole is not recommended with HIV protease inhibitors (such as atazanavir, nelfinavir) for which absorption is dependent on intragastric pH due to significant reduction in their bioavailability (see section "Administration details").

If co-administration of HIV protease inhibitors with PPI cannot be avoided, close clinical monitoring (e.g., viral 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). Concomitant use of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR (International Normalized Ratio). 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. In case of such concomitant use, the INR and prothrombin time should be monitored.

Methotrexate. It has been reported that concomitant use of high doses of methotrexate (e.g., 300 mg) and PPI increases the blood levels of methotrexate in some patients. Patients using high doses of methotrexate, e.g. those suffering from cancer or psoriasis, are recommended to suspend treatment with pantoprazole.

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 including oxidation by the CYP3A4 enzyme. There are no data on clinically significant interactions between pantoprazole and medicinal products that are also metabolized with these pathways (carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, oral contraceptives containing levonorgestrel and ethinyl estradiol).

An interaction of pantoprazole with other medicinal products which are metabolized using the same enzyme system cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not interfere with the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol), does not interfere with p-glycoprotein related with the absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Pantoprazole interaction studies have been performed by concomitantly administering pantoprazole with certain antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found between these drugs.

Medicinal products that inhibit or induce CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. 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 PPI that are metabolized through these enzyme systems.
Drug effects on laboratory test results. There have been reports of false-positive results of some urine screening tests for tetrahydrocannabinol in patients taking pantoprazole. Alternative confirmatory testing should be considered to verify positive results.

Administration details.
Impaired liver function. In patients with severe liver impairment, the liver enzymes should be monitored regularly, especially during long-term treatment. In case of a rise of the liver enzymes, the treatment should be discontinued (see section "Dosage and administration").
Concomitant use with NSAIDs. Prolonged use of the drug Zolopant®, 20 mg tablets, for prevention of gastric and duodenal ulcers caused by prolonged NSAIDs administration, should be limited in patients prone to frequent exacerbations of gastric and duodenal ulcers.
Evaluation of the risk level is conducted taking into account individual risk factors, including the age (> 65 years), history of gastric or duodenal ulcer development, as well as gastrointestinal bleedings.
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 weight loss, recurrent vomiting, dysphagia, hematemesis, anemia, melena) and when gastric ulcer is suspected or present, malignancy should be excluded. Further investigation should be performed if symptoms persist despite adequate treatment.
HIV protease inhibitors. Co-administration of pantoprazole is not recommended with HIV protease inhibitors (such as atazanavir) for which absorption is dependent on intragastric pH, due to significant reduction in their bioavailability (see section "Interaction with other medicinal products and other forms of interaction").
Vitamin B_{12} absorption. Pantoprazole may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body weight or risk factors for reduced vitamin B_{12} absorption upon long-term therapy or if respective clinical symptoms are observed.
Long-term treatment. In long-term treatment, especially when exceeding a treatment period of one year, patients should be kept under regular surveillance.
Gastrointestinal infections caused by bacteria. Treatment with pantoprazole 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 reported in patients treated with PPI 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 and may begin insidiously. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia (see section "Adverse reactions"). In most affected patients, hypomagnesemia (and hypomagnesemia-associated hypocalcemia and/or hypokalemia) improved after magnesium replacement and discontinuation of the PPI.
For patients requiring prolonged treatment or those taking PPI simultaneously with digoxin or medicinal products that may cause hypomagnesemia (e.g., diuretics), magnesium levels should be measured before starting PPI treatment and periodically during treatment.
Bone fractures. Long-term treatment (more than one year) with high doses of PPI may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other risk factors. Studies show that PPIs may increase the overall risk of fracture by 10-40 %. Some of this increase may be due to other 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.
Severe cutaneous adverse reactions. Severe cutaneous adverse reactions including erythema multiforme, Stevens — Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS-syndrome) which can be life-threatening or fatal, have been reported in association with pantoprazole with an unknown frequency (see section "Adverse reactions"). Patients should be advised of the signs and symptoms and monitored closely for the above skin reactions. If signs and symptoms suggestive of these reactions appear, pantoprazole should be withdrawn immediately and an alternative treatment considered.
Subacute cutaneous lupus erythematosus. The use of PPIs is associated with very rare cases of subacute cutaneous lupus erythematosus. 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 discontinuing pantoprazole. History of subacute cutaneous lupus erythematosus during previous therapy with a PPI may increase the respective risk when using other PPIs.
Effect on laboratory test results.
Increased chromogranin A (CgA) levels may interfere with investigations for neuroendocrine tumors. To avoid this interference, pantoprazole treatment should be temporarily withheld for at least 5 days before CgA measurements (see section "Pharmacodynamics"). If CgA and gastrin levels have not returned to the reference range after initial measurement, measurements should be repeated 14 days after cessation of PPI treatment.
This medicinal product contains less than 1 mmol (23 mg) of sodium/dose, therefore it is essentially sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy. The available data on the use of pantoprazole in pregnant women (approximately 300-1000 pregnancy outcomes) indicate no embryonal or feto-neonatal toxicity of the drug. Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of pantoprazole in pregnant women.
Breastfeeding. Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but such excretion has been reported. A risk to newborns/infants cannot be excluded. A decision on whether to discontinue breastfeeding or to discontinue/abstain from pantoprazole therapy should be made based on the benefit of breastfeeding for the child and the benefit of pantoprazole therapy for the woman.
Fertility. Pantoprazole did not impair fertility in animal studies.

Effect on reaction rate when driving motor transport or using other mechanisms. Pantoprazole has no or negligible effect on the reaction rate when driving motor transport or using other mechanisms. The possible development of adverse drug reactions such as dizziness and visual disturbances should be taken into account (see section "Adverse reactions"). In such cases driving or operating other mechanisms should be avoided.

Dosage and administration.
Zolopant®, 20 mg, tablets should be taken 1 hour before a meal, whole, without chewing or crushing, followed with water.
Recommended dosage.
Adults and children 12 years of age and above.
Symptomatic treatment of gastroesophageal reflux disease.
The recommended dose is 20 mg (1 tablet) of the drug Zolopant® per day. Usually, the symptoms of heartburn disappear after 2–4 weeks. If this period is not enough, the treatment is continued for a further 4 weeks. After the symptoms disappear, their recurrence may be controlled using 20 mg of the drug once daily, taking 1 tablet, when necessary. Switching to long-term therapy should be considered if deemed necessary in case adequate symptom control is not achieved.
Long-term treatment and prevention of relapse of reflux esophagitis.
For long-term treatment, the maintenance dose is 20 mg (1 tablet) of the drug Zolopant® per day, in case of exacerbation the dose may be increased to 40 mg per day. In this case, it is recommended to take Zolopant® 40 mg tablets. After elimination of the relapse, the dose may be reduced back to 20 mg per day.
Adults.
Prevention of gastric and duodenal ulcers caused by use of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at risk who require prolonged use of NSAIDs.
The recommended dose is 20 mg (1 tablet) of the drug Zolopant® per day.
Patients with impaired liver function. Patients with severe impairments of liver function should not exceed the dose of 20 mg (1 tablet) per day.
Patients with impaired renal function. Patients with impairments of renal function do not require dose adjustment.
Elderly patients do not require dose adjustment.

Children. The drug is not recommended for use in children under 12 years of age because of limited data on the safety and efficacy of the drug in this age group.

Overdose.
The symptoms of overdose are unknown.
Intravenous doses up to 240 mg over 2 minutes were well tolerated. Since pantoprazole is extensively bound to proteins it is not a readily dialysable drug.
In case of overdose with clinical signs of intoxication, symptomatic and supportive therapy is used. There are no recommendations on specific therapy.

Adverse reactions.
Adverse reactions were observed in approximately 5 % of patients.
The frequency of adverse reactions is classified as follows: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10000 and < 1/1000), very rare (< 1/10000), unknown (frequency cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Blood and lymphatic system disorders: rare: agranulocytosis; very rare: leukopenia, thrombocytopenia, pancytopenia.
Immune system disorders: rare: hypersensitivity reactions (including anaphylactic reactions, anaphylactic shock).
Metabolism and nutrition disorders: rare: hyperlipidemia and lipid increases (triglycerides, cholesterol); body weight changes; unknown: hyponatremia, hypomagnesemia (see section "Administration details"), hypocalcemia[1], hypokalemia[1].
Psychiatric disorders: uncommon: sleep disturbance; rare: depression (including exacerbations); very rare: disorientation (including exacerbation); unknown: hallucinations, confusion (especially in predisposed patients, as well as exacerbation of these symptoms in case of preexistence).
Nervous system disorders: uncommon: headache, dizziness; rare: taste disorders; unknown: paresthesia.
Eye disorders: rare: disturbances in vision/blurred vision.
Gastrointestinal disorders: common: fundic gland polyps (benign); uncommon: diarrhea, nausea, vomiting, abdominal distension, constipation, dry mouth, abdominal pain and discomfort; unknown: microscopic colitis.
Hepatobiliary system disorders: uncommon: liver enzymes increased (transaminases, γ-GT); rare: bilirubin increased; unknown: hepatocellular injury, jaundice, hepatocellular failure.
Skin and subcutaneous tissue disorders: uncommon: skin rash, exanthema, pruritus; rare: urticaria, angioedema; unknown: Stevens – Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), drug reaction with eosinophilia and systemic symptoms (DRESS-syndrome), erythema multiforme, photosensitivity, subacute cutaneous lupus erythematosus (see section "Administration details").
Musculoskeletal and connective tissue disorders: uncommon: fracture of the hip, wrist or spine (see section "Administration details"); rare: arthralgia, myalgia; unknown: muscle spasm[2].
Renal and urinary system disorders: unknown: tubulointerstitial nephritis (with possible development of renal failure).
Reproductive system and breast disorders: rare: gynecomastia.
General disorders: uncommon: asthenia, fatigue, malaise; rare: body temperature increased, peripheral edema.
[1] Hypocalcemia and/or hypokalemia may be associated with hypomagnesemia (see section "Administration details").
[2] Muscle spasm as a result of disturbance of the electrolyte balance.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua/.

Shelf-life.

3 years.

Storage conditions.
Store in the original package at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
14 tablets are in a blister. 1 blister is in a carton box.
10 tablets are in a blister. 3 blisters are in a carton box.

Conditions of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina str., 54.

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