

PACKAGE LEAFLET
for medical use of a medicinal product

OMEPRAZOLE- -DARNITSA

Qualitative and quantitative composition:

active substance: omeprazole;

1 capsule contains omeprazole pellets (equivalent to omeprazole) 20 mg;

List of excipients: mannitol (E 421), hypromellose, methacrylate copolymer dispersion, sodium lauryl sulfate, sodium hydrogen phosphate anhydrous, diethyl phthalate, sucrose, titanium dioxide (E 171), povidone, calcium carbonate, talc, polysorbate-80, sodium hydroxide.

Pharmaceutical form. Capsules. Capsules contain pellets.

Main physical and chemical properties: hard gelatin capsules with a dark red opaque body and an opaque lid of dark gray or black color, which contain spherical granules from white to white with a creamy pink shade.

Pharmacotherapeutic group. Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) Proton pump inhibitors. ATC code A02B C01.

Pharmacological properties.

Pharmacodynamics properties.

Omeprazole is an antiulcer antisecretory medicinal product. It easily penetrates the parietal cells of the gastric mucosa, concentrates in them and is activated at an acidic pH. The active metabolite, sulfenamide, suppresses H^+ , K^+ -ATP-ase of the secretory membrane of parietal cells (proton pump) by stopping the release of hydrogen ions into the stomach cavity and blocking the final stage of hydrochloric acid secretion. It dose-dependently reduces the level of basal and stimulated secretion, the total volume of gastric secretion and the release of pepsin. It effectively suppresses both night and day production of hydrochloric acid.

It has a bactericidal effect on *Helicobacter pylori* (*H. pylori*). Eradication of *H. pylori* with the simultaneous use of omeprazole and antibiotics allows to rapidly stop the symptoms of disease, achieve a high degree of healing of the affected mucous membrane, a stable long-term remission, and reduce the likelihood of bleeding from the gastrointestinal tract.

In reflux ulcerative esophagitis, the normalization of acid exposure in the esophagus and maintenance of an intragastric $pH > 4.0$ for 24 hours with a decrease in the destructive properties of the stomach contents (inhibition of the transition of pepsinogen to pepsin) contributes to the weakening of symptoms and complete healing of esophageal damage (the healing rate exceeds 90%). It is highly effective in the treatment of severe and complicated forms of erosive and ulcerative esophagitis, resistant to H_2 -blockers. Long-term maintenance therapy prevents recurrence of reflux esophagitis and reduces the risk of complications.

Pharmacodynamic properties.

After oral administration, the medicinal product is rapidly and in significant quantities absorbed from the digestive tract, but the bioavailability is no more than 50-55% (the effect of the "first pass" through the liver). Plasma protein binding (albumin and acid α_1 -glycoprotein) is very high, up to 95%.

After a single use of 20 mg of omeprazole, inhibition of gastric secretion occurs within the first hour, reaches a maximum after 2 hours and lasts within about 24 hours, the manifestation of the effect depends on the dose. The ability of parietal cells to produce hydrochloric acid is restored within 3 – 5 days after the end of therapy.

The medicinal product is transformed in the liver with the formation of at least 6 metabolites, characterized by a almost absent antisecretory activity.

It is excreted mainly by the kidneys in the form of metabolites (72 – 80%) and via the intestines (18 – 23%). The half-life is 0.5 – 1 hour (in case normal liver function) or 3 hours (with chronic liver diseases).

In elderly patients, a slight increase in bioavailability and a decrease in the rate of excretion are possible.

Clinical particulars.***Therapeutic indications.***

Benign gastric ulcer and duodenal ulcer, including those associated with the use of non-steroidal anti-inflammatory drugs; eradication of *Helicobacter pylori* (as part of combination therapy with antibacterial agents); gastroesophageal reflux disease, prevention of acidic stomach contents aspiration, Zollinger-Ellison syndrome; relief the symptoms of acid-dependent dyspepsia.

Contraindications.

Hypersensitivity to omeprazole, substituted benzimidazoles, or other components of the medicinal product. Omeprazole, like other proton pump inhibitors, should not be administered with nelfinavir and atazanavir.

Interaction with other medicinal products and other forms of interaction**The effect of omeprazole on the pharmacokinetics of other medicinal products.*****Medicinal products which absorption depends on the pH of the stomach.***

Inhibition of gastric secretion during the treatment with omeprazole and other medicinal products from the PPI group (proton pump inhibitors) may reduce or increase the absorption of medicinal products, the absorption of which depends on the pH of the stomach. As with other medicinal products that reduce intragastric acidity, absorption of medicinal products such as ketoconazole, itraconazole, and erlotinib may be decreased, while absorption of medicinal products such as digoxin may be increased during treatment with omeprazole. The simultaneous use of omeprazole (20 mg/day) and digoxin in healthy volunteers increased the bioavailability of digoxin by 10% (in two out of ten studied patients up to 30%).

Nelfinavir, atazanavir.

Plasma levels of nelfinavir and atazanavir decrease with concomitant use with omeprazole.

The simultaneous use of omeprazole and nelfinavir is contraindicated. The simultaneous use of omeprazole (40 mg once per day) reduced the average exposure of nelfinavir by about 40%, and the average exposure of the pharmacologically active metabolite M8 decreased by about 75 – 90%. Interaction may also be due to the inhibition of CYP2C19 activity.

Concomitant use of omeprazole with atazanavir is not recommended. The simultaneous use of omeprazole (40 mg 1 time per day) and atazanavir at a dose of 300 mg/ritonavir at a dose of 100 mg in healthy volunteers led to a 75% decrease in atazanavir exposure. Increasing the dose of atazanavir to 400 mg did not compensate for the effect of omeprazole on atazanavir exposure. Concomitant use of omeprazole (20 mg/day) with atazanavir at a dose of 400 mg/ritonavir at a dose of 100 mg in healthy volunteers led to an approximately 30% decrease in the exposure of atazanavir compared with atazanavir at a dose of 300 mg/ritonavir at a dose of 100 mg once a day.

Digoxin.

Simultaneous treatment with omeprazole (20 mg/day) and digoxin in healthy volunteers increased the bioavailability of digoxin by 10%. Cases of toxicity caused by the use of digoxin have been rarely reported. However, caution should be exercised when prescribing high doses of omeprazole to elderly patients. It is necessary to strengthen the therapeutic monitoring of digoxin by physicians.

Clopidogrel.

In the course of a cross-sectional clinical study, clopidogrel (loading dose of 300 mg, followed by 75 mg/day) as monotherapy and with omeprazole (80 mg simultaneously with clopidogrel) was used within 5 days. Following the simultaneous use of clopidogrel and omeprazole, the exposure of the active metabolite of clopidogrel decreased by 46% (day 1) and by 42% (day 5). The mean inhibition of platelet aggregation decreased by 47% (after 24 hours) and by 30% (day 5) when clopidogrel and omeprazole were used together. In another study, it was shown that administering of clopidogrel and omeprazole at different times did not interfere with their interaction, which is probably triggered by the inhibitory effect of omeprazole on CYP2C19. Controversial data regarding the clinical manifestations of this PK/PD interaction in terms of major cardiovascular diseases have been reported during observational and clinical studies.

Other medicinal products.

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole was significantly reduced, therefore, clinical efficacy may be weakened. Simultaneous use of the medicinal product with posaconazole and erlotinib should be avoided.

Medicinal products that are metabolized by CYP2C19.

Omeprazole is a mild inhibitor of CYP2C19, the main enzyme that metabolizes omeprazole. Thus, the metabolism of concomitant medicinal products, which are also metabolized with the participation of CYP2C19, may decrease, and the systemic exposure of these medicinal products may increase. Examples of such medicinal products are R-warfarin and other vitamin K antagonists, cilostazol, diazepam, and phenytoin.

In healthy volunteers, a pharmacokinetic/pharmacodynamic interaction was observed between clopidogrel (loading dose 300 mg/daily maintenance dose is 75 mg) and omeprazole (80 mg/day orally, i.e., the dose that 4-fold exceeds standard daily dose), resulting in a decrease in the exposure of the active metabolite of clopidogrel by an average of 46% and a decrease in the maximum inhibitory effect (ADP-induced) of platelet aggregation by an average of 16%. The clinical significance of this interaction remains unknown. As a precaution, the simultaneous use of omeprazole and clopidogrel should be avoided.

Cilostazol.

In healthy volunteers, the administration of omeprazole at a dose of 40 mg increased C_{max} and AUC of cilostazol by 18% and 26%, respectively, and one of its active metabolites by 29% and 69%, respectively.

Phenytoin.

Monitoring of the phenytoin concentration in blood plasma is recommended during the first two weeks after the start of treatment with omeprazole and if the dose of phenytoin has been adjusted, monitoring and subsequent adjustment of the dose of the medicinal product should be carried out after the end of treatment with omeprazole.

Unknown mechanism.

Saquinavir.

The simultaneous use of omeprazole with saquinavir/ritonavir led to an increase in the level of saquinavir in the blood plasma up to 70%, which was associated with a proper tolerance in HIV-infected patients.

Tacrolimus.

Following the simultaneous use of omeprazole, an increase in the level of tacrolimus in the blood serum has been reported. Increased monitoring of tacrolimus concentration as well as renal function (creatinine clearance) should be carried out and, if necessary, tacrolimus dose should be adjusted.

An increase in the level of methotrexate in some patients has been reported while concomitant administration with proton pump inhibitors. If it is necessary to use methotrexate in high doses, consideration should be given to the temporary withdrawal of omeprazole.

The effect of other medicinal products on the pharmacokinetics of omeprazole.

Inhibitors of CYP2C19 and/or CYP3A4.

Since omeprazole is metabolized by the CYP2C19 enzymes and CYP3A4, medicinal products that are known to inhibit the activity of CYP2C19 or CYP3A4, or both enzymes (for example, clarithromycin and voriconazole), can lead to an increase in the level of omeprazole in the blood serum as a result of slowing its metabolic rate. The simultaneous use of voriconazole led to a more than twofold increase in the exposure of omeprazole. Since high doses of omeprazole have been well tolerated, dose adjustment of omeprazole is generally not necessary. However, consideration should be given to dose adjustment for patients with severe hepatic impairment and when long-term treatment is indicated.

Omeprazole is also partially metabolized by CYP3A4, but does not suppress this enzyme. Thus, omeprazole does not affect the metabolism of medicinal products metabolized by CYP3A4, such as cyclosporine, lidocaine, quinidine, estradiol, erythromycin and budesonide.

CYP2C19 and/or CYP3A4 inducers.

Medicinal products that are known to induce the activity of CYP2C19 or CYP3A4, or both enzymes (for example, rifampicin and St. John's wort), can lead to a decrease in the level of omeprazole in blood plasma as a result of an acceleration of its metabolic rate.

Special warnings and precautions for use.

If patients with stomach ulcers or suspected gastric ulcers develop such alarming symptoms as significant weight loss not caused by diet, frequent vomiting, dysphagia, vomiting with blood or melena, the presence

of a malignant disease should be excluded, since administering the medicinal product can mask its symptoms and delay in making a diagnosis.

Concomitant use of atazanavir with proton pump inhibitors is contraindicated.

Omeprazole, like other acid-inhibiting substances, may reduce the absorption of vitamin B¹² (cyanocobalamin) due to hypo- or achlorhydria. This should be considered when treating patients with vitamin B₁₂ deficiency or at risk of decreased absorption of vitamin B₁₂ with prolonged therapy. In some cases, it may be advisable to monitor the level of vitamin B₁₂ in the blood plasma.

Omeprazole is a CYP2C19 inhibitor. At the beginning or at the end of treatment with omeprazole, the potential for interactions with medicinal product that are metabolized by CYP2C19, such as clopidogrel, should be considered.

For the treatment of chronic diseases in children, the medicinal product should not be used longer than recommended.

Administration of proton pump inhibitors may lead to a slight increase in the risk of digestive tract infections caused by pathogens such as *Salmonella* and *Campylobacter*.

With long-term therapy, especially in cases where the duration of treatment exceeds 1 year, patients should be monitored regularly and laboratory determination of the magnesium and calcium content in blood serum should be carried out.

There are reports of an increased risk of hypomagnesemia with long-term use of omeprazole (1 year or more) at usual doses of 20 – 40 mg per day.

Serum magnesium levels returned to normal after discontinuation of the medicinal product. The clinical picture of hypomagnesemia is characterized by: increased neuromuscular excitability, which is manifested by spasm of the muscles of the hands and feet, motor excitement; tachycardia, cardiac arrhythmia, increased blood pressure; dystrophic disorders in the form of trophic erosions and skin ulcers. The criterion for the diagnosis of hypomagnesemia is a decrease in the concentration of magnesium in the blood serum of less than 1 mEq/L. In addition, cases were identified when hypomagnesemia led to the development of hypocalcemia due to the suppression of parathyroid hormone secretion in conditions of low magnesium content in the body. In some patients, a severe course of hypocalcemia and hypomagnesemia was observed, accompanied by the development of convulsive syndrome, cardiac arrhythmias, tetany, mental disorders and severe vomiting leading to a deterioration in electrolyte balance.

Fertility, pregnancy and lactation.

The research results did not reveal any negative effect of omeprazole on the health of the fetus/newborn during pregnancy. The medicinal product may be used during pregnancy if, to the doctor's opinion, the expected benefit to the mother outweighs the possible risk to the fetus.

Omeprazole is excreted in small amounts in breast milk, but its effect on the child is unknown. Therefore, women should discontinue breast-feeding during the period of the medicinal product use.

Effects on ability to drive and use machines.

The effect of the medicinal product on the ability to drive vehicles or work with mechanisms is unlikely, but the possibility of such adverse reactions as dizziness and visual impairment should be taken into account.

Posology and method of administration.

It is administered orally before or during meals, without chewing or damaging the capsule, with a small amount of liquid. The dosage regimen depends on the type and severity of the disease and is set individually for each patient.

Adults and children over 12 years old.

Stomach and duodenal ulcer: the daily dose is 1 capsule. Usually the course of treatment for duodenal ulcers is 4 weeks, 8 weeks for stomach ulcers. If necessary, the daily dose can be increased to 2 capsules.

Treatment and prevention of duodenal and stomach ulcers, as well as gastroduodenal erosion and dyspeptic symptoms associated with the use of non-steroidal anti-inflammatory drugs: the recommended daily dose is 20 mg. The course of treatment is 4 – 8 weeks.

For the eradication of Helicobacter pylori: omeprazole is administered in a daily dose of 40 mg (20 mg 2 times per day) as part of complex therapy according to approved international schemes:

"Triple" therapy for duodenal ulcer: within 1 week, 2 times per day: amoxicillin 1 g and clarithromycin 500 mg; within 1 week, 2 times per day: clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg); within 1 week, 3 times per day: amoxicillin 500 mg and metronidazole 400 mg.

"Double" therapy for duodenal ulcer: within 2 weeks, 2 times per day: amoxicillin 750 mg – 1 g; within 2 weeks, 3 times per day: clarithromycin 500 mg.

"Dual" therapy for gastric ulcer: within 2 weeks, 2 times per day, amoxicillin 750 mg – 1 g.

Gastroesophageal Reflux Disease: the daily dose is 1 capsule; the course of treatment is 4 – 8 weeks. Patients with reflux esophagitis, resistant to treatment, are prescribed 2 capsules daily for 8 weeks.

Prevention of aspiration of acidic stomach contents: the recommended dose of omeprazole is 40 mg the night before and 40 mg 2 – 6 hours before anesthesia.

Zollinger-Ellison Syndrome: the initial dose of omeprazole, which is administered once in the morning, is 60 mg/day; if necessary, the daily dose is increased to 80 – 120 mg. The dose should be selected individually, taking into account the reaction of the body. If the daily dose exceeds 80 mg, it must be divided into 2 – 3 doses.

Acid-dependent dyspepsia: the daily dose is 10 – 20 mg once for 2 – 4 weeks. If after 4 weeks the symptoms do not disappear or reappear quickly, the patient's diagnosis should be revised. If it is necessary to use omeprazole in a single dose of less than 20 mg, a medicinal product with a lower content of the active substance is used.

Dose adjustment of omeprazole in elderly people and in patients with impaired renal function is not required.

In patients with impaired liver function, the maximum daily dose of omeprazole is 20 mg.

Children. In this dosage form, omeprazole is used for children from 5 years old with a body weight of at least 20 kg.

With reflux esophagitis, the course of treatment is 4 – 8 weeks;

with symptomatic treatment of heartburn and regurgitation of hydrochloric acid in gastroesophageal reflux disease: 2 – 4 weeks. The daily dose is 20 mg, if necessary, the daily dose may be increased to 40 mg.

If the child cannot swallow the capsule, open it and mix the contents with a small amount of apple juice or yogurt (approximately 10 ml). Make sure the child needs to swallow this mixture immediately after preparation.

It is possible to use omeprazole as part of a complex therapy for the eradication of *Helicobacter pylori* in children from 5 years old, but this therapy should be carried out with extreme caution under the close supervision of a physician. The course of treatment is 7 days, if necessary, the course of treatment is continued up to 14 days.

Treatment regimen:

- children weighing 30 – 40 kg: omeprazole 20 mg, amoxicillin 750 mg, clarithromycin 7.5 mg/kg² times a day for 7 days;
- children weighing more than 40 kg: omeprazole 20 mg, amoxicillin g, clarithromycin 500 mg 2 times per day for 7 days.

Children.

The medicinal product is used in children over 5 years of age as prescribed by a doctor, according to indications of reflux esophagitis and symptomatic treatment of heartburn and acid eructation in gastroesophageal reflux disease and for the treatment of duodenal ulcers caused by the presence of *H. pylori*, under the supervision of a doctor.

Overdose.

Very limited data are known regarding the effects of omeprazole overdose in humans. In the literature, doses of up to 560 mg of omeprazole have been described and isolated reports have been received about the achievement of a single oral dose of 2400 mg of omeprazole (120-fold higher than the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhea, and headache have been reported. Apathy, depression and confusion have also been reported on rare occasions.

The described symptoms are transient. The withdrawal rate does not change (first order kinetics) with increasing the dose.

Treatment. There is no specific treatment or antidote. Poorly excreted by dialysis. Gastric lavage, symptomatic and supportive therapy are indicated.

Undesirable effects.

The most common adverse events are headache, abdominal pain, constipation, diarrhea, bloating, and nausea/vomiting.

Adverse events have been ranked under headings of frequency using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$).

Eye disorders: Rare: blurred vision, visual impairment.

Ear and labyrinth disorders: uncommon: vertigo.

Respiratory, thoracic and mediastinal disorders: Rare: bronchospasm.

Gastrointestinal disorders: Common: abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting; rare: dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis.

Hepatobiliary disorders: Uncommon: increased activity of hepatic enzymes; rare: hepatitis, accompanied or not accompanied by jaundice; very rare: liver failure, encephalopathy in patients with known severe liver dysfunction.

Renal and urinary disorders: rare: interstitial nephritis.

Metabolic and nutritional disorders: Rare: hyponatremia; frequency unknown: hypomagnesemia, hypocalcemia.

Nervous system disorders: common: headache; uncommon: dizziness, paresthesia, sleep disturbances, feeling of weakness, drowsiness; rare: taste disturbances.

Psychiatric disorders Common: insomnia; rare: anxiety, slight disorientation, depression; very rare: aggression, hallucinations.

Blood and lymphatic system disorders: rare: thrombocytopenia, leukopenia; very rare: agranulocytosis, pancytopenia.

Immune system disorders: rare: hypersensitivity reactions, such as fever, angioedema and anaphylactic reaction / shock.

Skin and subcutaneous tissue disorders: Common: dermatitis, hyperemia, itching, rash, urticaria; rare: alopecia, photosensitivity; very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders: rare: arthralgia, myalgia; very rare: muscle weakness.

Reproductive system and breast disorders: very rare: impotence, gynecomastia.

Other: uncommon: malaise, peripheral edema; rare: excessive sweating.

The profile of side effects that were observed in children coincides with the profile in adults with both short-term and long-term therapy.

Shelf life.

2 years.

Special precautions for storage.

Store in the original package at a temperature not exceeding 25°C.

Keep out of the reach of children.

Nature and content of container.

By 10 capsules a contour blister package; 1 or 3 contour blister packages in a pack.

Category of release.

Prescription only medicine.

Manufacturer

PrJSC "Pharmaceutical firm "Darnitsa".

The manufacturer's location and address of the place of business.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

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