

PACKAGE LEAFLET
for medical use of a medicinal product

METODAR-DARNITSA

Qualitative and quantitative composition:

active substance: metoclopramide;

1 ml of solution contains metoclopramide hydrochloride 5 mg;

excipients: sodium chloride, disodium edetate, sodium sulfite anhydrous (E 221), propylene glycol, hydrochloric acid diluted, water for injections.

Pharmaceutical form. Solution for injection.

Basic physical and chemical properties: clear, colorless liquid.

Pharmacotherapeutic group. Peristalsis stimulants (propulsants).

ATC code A03F A01.

Pharmacological properties.

Pharmacodynamic properties.

Metoclopramide is the central dopamine antagonist which also exerts peripheral cholinergic activity.

The medicinal product combines two main effects: antiemetic effect and that of the accelerated gastric emptying and passing through the small intestine.

The antiemetic effect is caused by the impact on the central point of the brainstem (chemoreceptors - activating zone of the vomiting center), probably due to inhibition of dopaminergic neurons.

Increased peristalsis is also partially controlled by higher centers, but a mechanism of peripheral action, along with the activation of postganglionic cholinergic receptors and, possibly, inhibition of dopaminergic receptors of the stomach and small intestine may also be partially involved. Through the hypothalamus and the parasympathetic nervous system, it regulates and coordinates motor activity of the upper part of the gastrointestinal tract: increases the tone of the stomach and intestine, accelerates gastric emptying, reduces gastrostasis, prevents pyloric and esophageal reflux, encourages intestinal peristalsis. Normalizes secretion of bile, reduces the spasm of the Oddi sphincter without changing its tone, eliminates gallbladder dyskinesia.

Adverse effects apply mainly to extrapyramidal symptoms, which are based on the mechanism of dopamine-receptor-blocking impact on the central nervous system.

Long-term metoclopramide treatment may cause an increase in serum prolactin concentration due to the lack of dopaminergic inhibition of prolactin secretion. There have been case reports on galactorrhea and menstrual cycle disorders in women, in men - gynecomastia. However, these symptoms disappeared after discontinuation of treatment.

Pharmacokinetic properties.

Onset of action on the gastrointestinal tract occurs within 1-3 minutes after intravenous administration and 10-15 minutes after intramuscular injection. Antiemetic effect lasts for 12 hours. 13-30 % of the medicinal product binds to blood plasma proteins. The volume of distribution is 3.5 l/kg. Crosses blood-brain and placental barriers, enters breast milk. It is metabolized in the liver. Half-life is 4-6 hours. Part of the dose (approximately 20 %) is excreted in its original form, and the rest (approximately 80 %) after metabolic transformations in the liver is excreted by the kidneys in compounds with glucuronic or sulfuric acid.

In patients with severe renal failure, creatinine clearance is reduced to 70 %, and plasma half-life is increased (approximately 10 hours with creatinine clearance of 10-50 ml/min and 15 hours with creatinine clearance < 10 ml/minute).

Accumulation of metoclopramide was observed in patients with cirrhosis, which occurred along with a 50 % decrease in blood plasma clearance.

Clinical properties.***Therapeutic indications***

Adults: prevention of postoperative nausea and vomiting; nausea and vomiting caused by radiotherapy; symptomatic treatment of nausea and vomiting, including those associated with acute migraine.

Children: as a second-line medicinal product for preventing delayed nausea and vomiting caused by chemotherapy; treatment of postoperative nausea and vomiting.

Contraindications.

- Hypersensitivity to metoclopramide or to any other component of the medicinal product;
- gastrointestinal bleeding;
- mechanical intestinal obstruction;
- gastrointestinal perforation;
- confirmed or suspected pheochromocytoma (due to the risk of severe hypertension attacks);
- tardive dyskinesia, due to neuroleptics or metoclopramide, in anamnesis;
- epilepsy (increased frequency and intensity of seizures);
- Parkinson's disease;
- concurrent use with levodopa or dopaminergic agonists;
- - established methemoglobinemia in the use of metoclopramide or deficiency of NADH-cytochrome-b5-reductase in anamnesis;
- prolactin-dependent tumors;
- increased convulsive readiness (extrapyramidal motor disturbances);
- age of the patient under 1 year (due to the risk of extrapyramidal disturbances).

Due to the fact that the medicinal product contains sodium sulfite, it should not be administered to the sulfite-hypersensitive asthmatic patients.

Interaction with other medicinal products and other types of interaction.**Contraindicated combinations.**

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism.

Combinations to be avoided.

Alcohol enhances the sedative effect of metoclopramide.

Attention should be drawn to the following combinations.

When used concurrently with oral medicines, such as paracetamol, metoclopramide may affect their absorption caused by gastric motility being affected.

Anticholinergics and morphine derivatives: anticholinergics and morphine derivatives have mutual antagonism with metoclopramide to affect motor activity of the digestive tract.

Inhibitors of the central nervous system (morphine derivatives, neuroleptics, sedative antihistamine-H1 receptor blockers, sedative antidepressants, barbiturates, clonidine and related medicinal products): potentiate metoclopramide effect.

Neuroleptics: metoclopramide in combination with other neuroleptics may induce a cumulative effect and extrapyramidal disorders.

Serotonergic medicinal products: administration of metoclopramide in combination with serotonergic medicinal products, such as selective serotonin reuptake inhibitors (SSRIs), may increase the risk of serotonin syndrome.

Digoxin: metoclopramide may decrease digoxin bioavailability. Concentration of digoxin in the blood plasma should be closely monitored.

Cyclosporine: metoclopramide increases cyclosporin bioavailability (C_{max} by 46 % and effect by 22 %). Concentration of cyclosporin in blood plasma should be closely monitored. Clinical consequences of this phenomenon have not been definitively identified.

Mivacurium and Suxamethonium: injection of metoclopramide may increase the duration of the neuromuscular block (due to inhibition of blood plasma cholinesterase).

Potent CYP2D6 inhibitors: metoclopramide exposure levels enhance while it is used with potent CYP2D6 inhibitors, such as fluoxetine and paroxetine. Although the clinical significance of this is

not definitively known, patients should be monitored for adverse reactions. Metoclopramide may prolong *succinylcholine* action.

Since injection solution contains sodium sulfite, thiamine (vitamin B₁), taken concomitantly with metoclopramide, can be rapidly degraded in the body.

Special precautions for use.

The medicinal product should not be used in the treatment of chronic diseases such as gastroparesis, dyspepsia and gastroesophageal reflux disease, or as an adjunct for surgical or radiological procedures.

Patients under 30 years of age are more prone to develop dystonic and dyskinetic disorders in the metoclopramide treatment.

Care should be taken when prescribing the medicinal product to elderly patients due to the frequent occurrence of parkinsonism.

Neurological disorders.

Extrapyramidal disorders may occur, especially in children, and/or at high doses. These reactions are usually observed in early treatment and may occur after a single use. If extrapyramidal symptoms develop, metoclopramide must be immediately withdrawn. In general, these effects disappear completely after the termination of treatment, but may require symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults). Between each administration of metoclopramide, even in the event of vomiting and rejection of the dose, it is necessary to maintain at least a 6-hour interval in order to avoid an overdose.

Long-term treatment with metoclopramide may cause tardive dyskinesia, which is potentially irreversible, especially in the elderly. Treatment should not last longer than 3 months because of the risk of tardive dyskinesia. Treatment should be discontinued if there are clinical signs of tardive dyskinesia.

Administration of metoclopramide in combination with neuroleptics, as well as metoclopramide monotherapy, was reported to develop malignant neuroleptic syndrome. In the event of symptoms of a malignant neuroleptic syndrome, administration of metoclopramide must be discontinued immediately and appropriate treatment initiated.

Special care should be given to patients with concomitant neurological diseases, as well as to patients being treated with other medicinal products affecting central nervous system.

Administration of metoclopramide may also exacerbate the symptoms of Parkinson's disease.

Methemoglobinemia.

There have been case reports of methemoglobinemia that may be due to a deficiency of NADH-cytochrome-b5-reductase. In such cases, administration of metoclopramide must be terminated immediately and appropriate measures taken (for example, treatment with methylene blue).

Heart disorders.

There have been reports of severe adverse reactions from the cardiovascular system, including cases of acute vascular insufficiency, severe bradycardia, cardiac arrest, and the QT interval prolongation that have been observed after taking metoclopramide in the form of an injection, especially after administration.

Intravenously, the medicinal product should be given in the form of a slow bolus injection (minimum for 3 minutes) to reduce the risk of adverse reactions (e.g., hypotension, akathisia).

Impaired renal and hepatic function.

Patients with impaired renal function or severe hepatic impairment are recommended dose reduction.

At-risk patients, namely, elderly patients with cardiac conduction disorders, unadjusted electrolyte imbalance or bradycardia, and patients being treated with other medicinal products that extend the QT interval, should be administered the medicament cautiously.

The medicinal product should not be used for the treatment of chronic diseases such as gastroparesis, dyspepsia and gastroesophageal reflux disease, or as an adjunct in surgical or radiological procedures. Ampoules taken from the package cannot be exposed to the sun for long.

Fertility, pregnancy and lactation.

Pregnancy.

A large amount of data regarding pregnant women (over 1000 medicinal product results) indicates that there is no toxicity that results in malformations or fetotoxicity. In the event of clinical need, metoclopramide can be used during pregnancy. Because of the pharmacological properties (as in other neuroleptics) in the case of metoclopramide, occurrence of extrapyramidal syndrome in a newborn cannot be ruled out at the final stages of pregnancy. Administration of metoclopramide must be avoided at the final stages of pregnancy. When using metoclopramide, it is necessary to observe the newborns.

Lactation.

Metoclopramide passes into breast milk in small amounts. Therefore, it is not advisable to use metoclopramide during breastfeeding. It is necessary to consider the possibility of metoclopramide withdrawal in breastfeeding women.

Effects on ability to drive and use machines

When using the medicinal product, one should avoid potentially hazardous activities that require increased attention (driving vehicles, operating other mechanisms).

Posology and method of administration

Inject the solution for injections intramuscularly or intravenously as a slow bolus injection for at least 3 minutes.

Use 0.9 % sodium chloride solution, 5 % glucose solution as the solvent.

Adults.

Administer the medicament in a dose of 10 mg to 3 times a day. The maximum daily dose is 30 mg or 0.5 mg/kg body weight.

The use of injection forms should take the shortest possible period of time, with the fastest possible transition to the use of oral or rectal forms of metoclopramide.

Children.

When used to prevent postoperative nausea and vomiting, metoclopramide should be applied after surgery.

The recommended dose of metoclopramide is 0.1-0.15 mg/kg body weight to 3 times a day. The maximum daily dose is 0.5 mg/kg body weight. If it is necessary to continue the use of the medicament, at least 6-hour intervals should be maintained.

Dosage regimen

Age, years	Body weight, kg	Single dose, mg	Frequency
1–3	10–14	1	Up to 3 times a day.
3–5	15–19	2	Up to 3 times a day.
5–9	20–29	2,5	Up to 3 times a day.
9–18	30–60	5	Up to 3 times a day.
15–18	>60	10	Up to 3 times a day.

The maximum duration of metoclopramide application for the treatment of manifested postoperative nausea and vomiting is 48 hours.

The maximum duration of the metoclopramide application to prevent delayed nausea and vomiting induced by chemotherapy is 5 days.

Patients with impaired renal function.

In patients with the end-stage renal dysfunction (creatinine clearance ≤ 15 ml/min) metoclopramide dose should be reduced by 75 %.

In patients with moderate and severe renal dysfunction (creatinine clearance 15-60 ml/min), metoclopramide dose should be reduced by 50 %.

Patients with hepatic insufficiency, due to the half-life extension, should be administered a half dose.

Elderly patients.

Consideration should be given to reducing the dose in elderly patients, due to decreased renal and hepatic function caused by the age.

Duration of treatment.

In order to minimize the risks of adverse reactions in the nervous system and other adverse reactions, the medicament should only be used for short-term treatment (up to 5 days).

Children.

Metoclopramide is contraindicated in children under 1 year of age.

Overdose.

Symptoms: drowsiness, lowered consciousness, confusion, irritability, anxiety and its enhancement, convulsions, extrapyramidal motor disorders, cardiovascular system dysfunction with bradycardia and increase or decrease in blood pressure, hallucinations, respiratory and cardiac arrest, dystonic reactions. There have been single cases reports of methemoglobinemia.

Treatment: extrapyramidal disorders are eliminated by the slow administration of the biperidene antidote. In case of large doses of metoclopramide, it must be removed from the gastrointestinal tract by gastric lavage or taking activated charcoal and sodium sulfate. The vital functions of the body shall be monitored until complete disappearance of poisoning symptoms.

Undesirable effects.

Gastrointestinal disorders: nausea, dyspepsia, dry mouth, constipation. When using metoclopramide in doses exceeding the daily dose, patients may experience diarrhea.

Nervous system disorders:

- extrapyramidal reactions, usually dystonia (including very rare cases of dyskinetic syndrome), especially in children and patients under the age of 30, the risk of which increases with an excess of the daily dose of 0.5 mg/kg body weight: spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, bulbar type of speech, spasm of extraocular muscles including oculogyric crises, involuntary spasmodic movements, particularly in the head, neck and shoulders, tonic blepharospasm, unnatural positions of the head and shoulders, opisthotonus, muscular hypertonus;
- parkinsonism (tremor, muscle twitching, bradykinesia, muscle rigidity, akinesia, mask-like face) after long-term metoclopramide treatment in some elderly patients, as well as in patients with renal failure;
- tardive dyskinesia, which may be irreversible, may occur with long-term metoclopramide therapy, mainly in elderly patients (especially women), in patients with diabetes mellitus and usually develops after discontinuation of the medicinal product. It is manifested by involuntary movements of the tongue, face, mouth, jaw, and sometimes involuntary movements of the torso and/or extremities;
- neuroleptic malignant syndrome, including hyperpyrexia, altered consciousness, muscle rigidity, autonomic nervous system dysfunction, and elevated serum creatine phosphokinase levels. This syndrome is potentially lethal, should it occur, metoclopramide administration must be immediately discontinued and therapy initiated urgently (dantrolene, bromocriptine);
- fever, headache, dizziness, drowsiness, fatigue, asthenia, increased fatigability, depressed consciousness, fear, anxiety, confusion, tinnitus, akathisia.

Also, there is a risk of acute (short-term) neurological disorders, which is higher in children.

Psychiatric disorders: depression, hallucinations, confusion, anxiety, restlessness.

Cardiac disorders: bradycardia, especially in intravenous application, cardiac arrest within a short time after the injection, which may be a consequence of bradycardia, atrioventricular blockade, blockade of the sinus node, especially when administered intravenously, prolongation of the QT interval, supraventricular extrasystole, ventricular extrasystole, ventricular "pirouette" type tachycardia, arterial hypotension, shock, fainting with intravenous administration, acute arterial hypertension in patients with pheochromocytoma.

There have been individual reports on the possibility of developing severe cardiovascular reactions due to the use of metoclopramide, particularly when administered intravenously.

Blood and lymphatic system disorders: methemoglobinemia, which may be associated with a deficiency of NADH-cytochrome-b5-reductase, especially in infants, sulfhemoglobinaemia, which is associated mainly with the co-administration of high doses of medicinal products that release sulfur.

Immune system disorders: hypersensitivity reactions including anaphylactic reactions, including Quincke's edema, anaphylactic shock. Due to the presence of sodium sulfite in the dosage form, individual cases of hypersensitivity may occur, especially in asthmatic patients, such as nausea, vomiting, wheezing, an acute asthma attack, impaired consciousness or shock. These reactions may have an individual course.

Skin and subcutaneous tissue disorders: hypersensitivity reactions, including: skin rash, hyperemia and pruritus, urticaria.

Reproductive system and breast disorders: after a prolonged therapy with the medicinal product hyperprolactinemia, gynecomastia, galactorrhea, or menstrual disorder, amenorrhea may occur due to the stimulation of prolactin secretion; should these phenomena develop, discontinue administration of metoclopramide.

Investigations: elevated liver enzymes.

In adolescents and patients with severe renal impairment (renal failure) resulting in a delay of metoclopramide excretion, particular attention must be paid to the development of side effects. In the event of their occurrence, the use of the medicament should be discontinued immediately.

The risk of developing adverse reactions in the nervous system increases with the use of the medicinal product in high doses and its long-term use.

Shelf life. 4 years.

Special precautions for storage.

Store in the original package at temperature not above 25 °C. Keep out of reach of children. Do not freeze.

Incompatibilities.

Metoclopramide injection solution cannot be mixed with alkaline infusion solutions.

Nature and contents of container.

2 ml in an ampoule; 5 ampoules in a blister; 1 or 2 blisters 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.

Date of the last revision.

01.08.2017