

PACKAGE LEAFLET
for medical use of a medicinal product

NEOPHYLLINE

Qualitative and quantitative composition:

active substance: theophylline;

1 tablet contains theophylline monohydrate equivalent to theophylline 300 mg;

excipients: lactose monohydrate, ammonio methacrylate copolymer dispersion, methacrylate copolymer dispersion, magnesium stearate, talc.

Pharmaceutical form. Prolonged release tablet.

Basic physical and chemical properties:

300 mg tablets – white, flat-cylindrical, beveled tablets with a breaking line;

Pharmacotherapeutic group. Agents for systemic use in obstructive airway diseases. Xanthines. Theophylline. ATC code R03D A04.

Pharmacological properties.

Pharmacodynamic properties.

Theophylline is a bronchodilator of the methylxanthine group. The mechanism of action is mainly due to the blocking of adenosine receptors, inhibition of phosphodiesterases, an increase intracellular cAMP, a decrease of calcium ions in the intracellular concentration resulting to relaxation the smooth muscles of the bronchus, gastrointestinal tract, biliary tract, uterus, coronary, cerebral and pulmonary vessels, and decreasing the peripheral vascular resistance; increasing the tonus of the respiratory muscles (intercostal muscles and diaphragm), reducing the resistance of the pulmonary vessels and blood oxygenation improves, activation the respiratory center of the medulla oblongata, increasing its sensitivity to carbon dioxide, improving the alveolar ventilation leading to decreased severity and frequency of apnoea episodes; relieving the angiospasm, improving the collateral blood flow and blood oxygen saturation, reducing the perifocal and general brain edema, reducing the liquor and, accordingly, intracranial pressure; improving the rheological properties of blood, relieving the thrombogenesis, inhibition the platelet aggregation (by suppressing platelet activation factor and prostaglandin F_{2α}), normalisation the microcirculation; it has an anti-allergic effect, suppressing mast cell degranulation and reducing the levels of allergy mediators (serotonin, histamine, leukotrienes); increaseing the renal blood flow, has diuretic action due to decreasing the tubular reabsorption, increasing the excretion of water, chlorine ions, sodium.

Pharmacokinetic properties.

Following oral administration, theophylline is completely absorbed in the gastrointestinal tract, with a bioavailability of approximately 90 %. Following administration prolonged release tablets, theophylline peak concentration is reached after 6 hours. In healthy adults binding to plasma proteins is approximately 60 % and 35 % in patients with liver cirrhosis. Theophylline passes through histohematic barriers with distribution in tissues. Approximately 90 % of theophylline is metabolized in the liver with the participation of several cytochrome P450 isoenzymes to inactive metabolites 1,3-dimethyluric acid, 1-methyluric acid and 3-methylxanthine. It is excreted mainly by the kidneys as metabolites; in adults and children approximately 13 % and 50 % of the drug is excreted unchanged,

respectively. Partially excreted into breast milk. Elimination half-life of theophylline depends on age and comorbidities and is 6-12 hours in adult patients with bronchial asthma; 3-4 hours in children aged from 6 months; 4-5 hours in smokers; more than 24 hours in elderly and patients with heart failure, impaired liver function, pulmonary edema, chronic obstructive pulmonary diseases and bronchitis and these states are requiring appropriate correction of the interval between the drug administrations.

Therapeutic concentrations of theophylline in the blood are 10-20 µg/ml to achieve a bronchodilator effect and 5-10 µg/ml for stimulation the respiratory center. Toxic levels are considered to be higher than 20 µg/ml.

Clinical particulars.

Therapeutic indications.

- Bronchial asthma.
- Chronic obstructive pulmonary diseases (chronic obstructive bronchitis, pulmonary emphysema).
- Pulmonary hypertension.
- Central sleep apnea syndrome.

Contraindications.

Hypersensitivity to the components of the drug and other xanthine derivatives (caffeine, pentoxifylline, theobromine), acute heart failure, angina pectoris, acute myocardial infarction, acute cardiac arrhythmias, paroxysmal tachycardia, extrasystole, severe arterial hyper- and hypotension, generalized vascular atherosclerosis, pulmonary oedema, hemorrhagic stroke, glaucoma, retinal hemorrhage, history of bleeding, gastric and duodenal ulcers (in exacerbation stage), gastroesophageal reflux, epilepsy, increased convulsive readiness, uncontrolled hypothyroidism, hyperthyroidism, thyrotoxicosis, impaired liver and/or kidney function, porphyria, sepsis, in children coadministration with ephedrine.

Interaction with other medicinal products and other forms of interaction.

Medicinal products that increase theophylline clearance: aminoglutethimide, antiepileptic drugs (for example, phenytoin, carbamazepine, primidone), magnesium hydroxide, isoproterenol, lithium, moracizine, rifampicin, ritonavir, sulfinpyrazone, barbiturates (especially phenobarbital and pentobarbital). The effect of theophylline may also be less significant in smokers. In patients who are concomitantly taking one or more of the above mentioned medications with theophylline, the serum concentration of theophylline should be monitored and the dose adjusted, if necessary.

Medicinal products that reduce theophylline clearance: allopurinol, acyclovir, carbimazole, phenylbutazone, fluvoxamine, imipenem, isoprenaline, cimetidine, fluconazole, furosemide, pentoxifylline, disulfiram, interferon, nizatidine, calcium antagonists (verapamil, diltiazem), amiodarone, paracetamol, probenecid, ranitidine, tacrin, propafenone, propranolol, oxpentifylline, isoniazid, lincomycin, methotrexate, zafirlukast, mexiletine, fluoroquinolones (ofloxacin, norfloxacin, when using ciprofloxacin, it is necessary to reduce the dose at least by 60 %, enoxacin – by 30 %), macrolides (clarithromycin, erythromycin), ticlopidine, thiabendazole, viloxazine hydrochloride, oral contraceptives, flu vaccine. In patients who are concomitantly taking one or more of the above medications with theophylline, the serum concentrations of theophylline should be monitored and the dose reduced, if necessary.

The plasma concentration of theophylline can be reduced when theophylline is co-administered with herbal medicines containing St. John's wort (*Hypericum perforatum*).

Concomitant use of theophylline and phenytoin may lead to decreased levels of phenytoin.

Ephedrine enhances the effect of theophylline.

The combination of theophylline and fluvoxamine should be avoided. If this combination is considered necessary, patients should receive one-half of theophylline dose and plasma concentrations of theophylline should be monitored.

Combinations of theophylline and adenosine, benzodiazepine, halothane and lomustine should be used with special cautions. Halothane anesthesia may cause serious cardiac arrhythmias in patients taking theophylline.

Concomitant use of theophylline and large amounts of food and beverages containing methylxanthines (coffee, tea, cocoa, chocolate, Coca-Cola and similar tonic drinks), medicines containing xanthine derivatives (caffeine, theobromine, pentoxifylline), α and β -adrenergic agonists (selective and non-selective), glucagon, should be avoided due to potentiation of the theophylline effects.

Co-administration of theophylline with beta-blockers may antagonise its bronchodilating effect; with ketamine, quinolones – reduces the convulsive threshold; with adenosine, lithium carbonate and beta-receptor antagonists – reduces the effectiveness of these drugs; with doxapram – may cause stimulation of the central nervous system.

Theophylline may enhance the effect of diuretics and reserpine.

Concomitant use of theophylline and beta-receptor antagonists should be avoided as theophylline may fail to be effective.

There are conflicting reports concerning the potentiation of theophylline by influenza.

Xanthines may potentiate hypokalemia caused by therapy with beta-adrenergic agonists, steroids, diuretics, and hypoxia. This applies to hospitalized patients with severe asthma and there is a need to monitor serum potassium levels.

Special warnings and precautions for use.

Theophylline should be prescribed only if absolutely necessary and with caution to patients with unstable angina, heart diseases that may be accompanied by tachyarrhythmia; hypertrophic obstructive cardiomyopathy, impaired kidney and liver function, hyperthyroidism, acute porphyria, chronic alcoholism and lung diseases, patients with a history of peptic ulcer disease and patients over 60 years of age.

The use of theophylline in severe vascular atherosclerosis, sepsis is possible with caution, under physician's supervision, if there are indications for theophylline use. Restriction on the use of theophylline in gastroesophageal reflux is associated with the effect on the smooth muscles of the cardioesophageal sphincter, which may worsen the condition the patients with gastroesophageal reflux by increasing reflux.

Tobacco smoking and alcohol consumption may lead to increasing the clearance of theophylline and, accordingly, to decreasing its therapeutic effect and therefore its higher doses may be needed.

During treatment with theophylline, it is necessary to monitor carefully and reduce the dose during treatment of patients with heart failure, chronic alcoholism, impaired liver function (especially cirrhosis), with low concentration of oxygen in the blood (hypoxemia), with fever, patients with pneumonia or viral infections (especially flu) due to a possible decrease in theophylline clearance. At the same time, it is necessary to monitor plasma levels of theophylline that exceed the norm.

Monitoring is necessary when treating with theophylline the patients with peptic ulcer disease, cardiac arrhythmia, arterial hypertension, other cardiovascular diseases, hyperthyroidism, or acute febrile conditions.

Administration of theophylline should be avoided in patients with a history of seizures and alternative treatment should be considered.

Increased attention should be paid when administering the drug to patients suffering from insomnia and elderly men with a previous history of prostate enlargement due to the risk of urinary retention.

If considered necessary to use aminophylline (theophylline-ethylenediamine) in patients who have already used theophylline, monitoring the plasma levels of theophylline should be reinstituted.

Due to the inability to guarantee the bioequivalence of individual drugs containing theophylline with prolonged release, switching from therapy with Neophylline prolonged-release tablets to another prolonged release drug of the xanthine group should be carried out by re-titration of the dose and after clinical evaluation.

Special care should be taken during treatment with theophylline in severe asthma. In such situations, it is recommended to monitor the serum levels of potassium.

Worsening of asthma symptoms requires urgent medical care. In the case of an acute asthmatic attack in patients receiving prolonged-acting theophylline, intravenous aminophylline should be prescribed very carefully.

Half of the recommended loading dose of aminophylline (usually 6 mg/kg) should be administered with caution, i.e. 3 mg/kg.

If it is necessary to use theophylline in children with pyrexia or with a history of epilepsy and seizures, their clinical condition should be carefully monitored and plasma theophylline levels should be monitored. Theophylline is not the drug of choice in children with bronchial asthma. Theophylline may change some laboratory parameters: increase the amount of fatty acids and the level of catecholamines in the urine.

In case of adverse reactions, it is necessary to monitor the level of theophylline in the blood.

Relevant information on excipients.

This medicinal product contains lactose for this reason it should not be used in patients with rare hereditary forms of galactose intolerance, lactase deficiency, or glucose-galactose malabsorption syndrome.

Fertility, pregnancy and lactation.

Pregnancy.

Theophylline passes through the placenta.

The use of the drug during pregnancy is possible in the absence of a safe alternative, if the expected benefit to the mother exceeds the potential risk to the fetus. In pregnant women, it is necessary to determine the concentration of theophylline in the blood serum more often and adjust the dose accordingly. Theophylline should be avoided at the end of pregnancy period, as it can inhibit uterine contractions and cause tachycardia in the fetus.

Lactation.

Theophylline penetrates into breast milk, so therapeutic serum concentrations can be achieved in children. Its use in breast-feeding mothers is allowed only if the intended benefit to the mother exceeds the risk to the newborn.

Theophylline may cause increased irritability in the newborn, so the therapeutic dose of theophylline should be as low as possible.

Breast-feeding should be carried out immediately before taking the drug. Any effects of theophylline in infants should be carefully monitored. If higher therapeutic doses are required, breast-feeding should be discontinued.

Fertility.

There are no clinical data on human fertility. From preclinical data, it is known about the adverse effects of theophylline on male and female fertility.

Effects on ability to drive and use machines.

Given that sensitive patients may experience adverse reactions (dizziness) when using the drug, it is necessary to refrain from driving vehicles and other work that requires concentration of attention while on treatment with the drug.

Posology and method of administration.

The drug should be taken orally 30-60 minutes before meals or 2 hours after meals, with a sufficient amount of liquid. A 300 mg tablet can be divided in half, but must not be crushed, chewed, or dissolved in water. In some cases, to reduce the irritating effect on the gastric mucosa, the drug should be taken during meal or immediately after a meal.

The dosage regimen to be prescribed individually, depending on the patient's age, body weight and metabolic peculiarities.

The initial daily dose for adults and children over 12 years of age with a body weight greater than 45 kg is 300 mg (300 mg tablet once a day). After 3 days of taking the drug, the daily dose can be increased to 450 mg (1½ tablets of 300 mg), after another 3 days of treatment, if necessary, the daily dose can be increased to 600 mg (1 tablet of 300 mg 2 times a day).

Dose increase is possible only in case of good tolerability.

For children 6 to 12 years with a body weight of 20 –45 kg, the daily dose is 150 mg (½ tablet of 30 mg 1 time a day). After 3 days of taking the drug, the daily dose can be increased to 300 mg (½ tablet of 300 mg 2 times a day), after another 3 days of treatment, the daily dose can be increased to 450-600 mg (1½ tablets of 300 mg 1 time a day or 1 tablet of 300 mg 2 times a day).

For elderly patients with cardiovascular diseases, the recommended daily dose of the drug is 8 mg/kg of body weight. The maximum therapeutic effect appears 3-4 days after the start of treatment.

For patients who smoke, the daily dose can be gradually increased to 900-1050 mg (3–3½ tablets of 300 mg).

Patients with central sleep apnea syndrome can take a single dose of the drug at night.

Further dose increasing is recommended based on determining the serum concentrations of theophylline.

The dosage is selected individually, but usually tablets are taken 2 times a day. In patients with the most severe clinical manifestation of symptoms, it is appropriate to use higher morning or evening doses.

For patients whose symptoms persist at night or during the day, regardless of other therapy or if they have not received theophylline, therapy may be supplemented with the recommended single morning or evening daily dose of theophylline.

When prescribing high doses during treatment, theophylline concentrations in blood plasma should be monitored (the therapeutic concentration should be in the range of 10-15 µg/ml).

The total dose should not exceed 24 mg/kg of body weight for children and 13 mg/kg for adults. Despite this, determining the level of theophylline in plasma 4-8 hours after administration and at least 3 days after each dose change allows accurate assessment of the need for a specific dose due to the presence of significant individual differences in the degree of elimination in individual patients.

The table below can be used as a guide for correct dosage.

Theophylline concentration in plasma (µg/ml)	Result	Referral (if clinically indicated)
Less than 10	Too low	Dose increased by 25 %
10–20	Normal	Maintenance dose
20–25	Too high	Dose decreased by 10 %
25–30	Too high	Skip the next dose and then reduce the dose by 25 %
Over 30	Too high	Skip the next two doses and then reduce the dose by 50 %

Children.

The drug should not be used in children under 6 years of age with a body weight of less than 20 kg.

Overdose.

Overdose is observed if the concentration of theophylline in the blood serum exceeds 20 mg/mL (110 µmol/L).

Symptoms. Severe symptoms may develop 12 hours after an overdose of prolonged-release dosage forms.

Digestive tract: nausea, vomiting (often severe), epigastric pain, diarrhea, hematemesis, pancreatitis.

Central nervous system: delirium, agitation, anxiety, dementia, toxic psychosis, tremor, increased limb reflexes and convulsions, muscle hypertension. In very severe cases, a coma may develop.

Cardiovascular system: sinus tachycardia, ectopic rhythm, supraventricular and ventricular tachycardia, arterial hypertension/hypotension, a sharp decrease in blood pressure.

Metabolic disorders: metabolic acidosis, hypokalemia (due to the transition of potassium from plasma to cells, it can develop quickly and in severe form), hypophosphatemia, hypercalcemia, hypomagnesemia, hyperglycemia, rhabdomyolysis.

Other: respiratory alkalosis, hyperventilation, acute renal failure, dehydration, or increase of other adverse reactions.

Treatment. Discontinuation of the drug, gastric lavage, per os – activated charcoal, osmotic laxatives (within 1-2 hours after overdose); hemodialysis. Monitoring serum levels of theophylline until normalization of indicators, ECG and renal function monitoring.

In convulsive syndrome, the use of diazepam is indicated.

Patients who do not suffer from bronchial asthma may use non-selective beta-blockers if severe tachycardia occurs. In severe cases, it is possible to accelerate the elimination of theophylline by hemosorption or hemodialysis.

Hypokalemia should be avoided/prevented. In case of hypokalemia, an urgent intravenous infusion of potassium chloride solution, monitoring plasma levels of potassium and magnesium should be initiated.

If large amounts of potassium are used, hyperkalemia may develop during recovery. If the plasma level of potassium is low, the plasma concentration of magnesium should be measured as soon as possible.

Antiarrhythmic drugs with anticonvulsant effects, such as lidocaine, should be avoided in ventricular arrhythmias because of risk of exacerbation of seizures. Antiemetics such as metoclopramide or ondansetron should be used to relieve vomiting.

In tachycardia with adequate cardiac output, it is better not to use treatment.

In case of life-threatening overdose with cardiac arrhythmias – administration of propranolol to non-asthmatic patients (1 mg for adults and 0.02 mg/kg of body weight for children). This dose can be used every 5-10 minutes until the heart rate normalizes, but do not exceed the maximum dose of 0.1 mg/kg of body weight. Propranolol can cause severe bronchospasm in patients with asthma, therefore verapamil should be used in such cases.

Further treatment depends on the degree of overdose and the course of intoxication, as well as on the existing symptoms.

Undesirable effects.

Adverse reactions are usually observed at plasma concentrations of theophylline > 20 µg/ml.

Respiratory, thoracic and mediastinal disorders: respiratory rate increase.

Gastrointestinal disorders: heartburn, decreased appetite/anorexia with prolonged use, nausea, vomiting, abdominal pain, diarrhea, gastroesophageal reflux, exacerbation of peptic ulcer disease, stimulation of gastric acid secretion, intestinal atony, digestive tract hemorrhages.

Hepatobiliary disorders: impaired liver function, jaundice.

Renal and urinary disorders: increased diuresis, especially in children, urinary retention in elderly men.

Metabolism and nutrition disorders: hypokalemia, hypercalcemia, hyperuricemia, hyperglycemia, rhabdomyolysis, metabolic acidosis.

Nervous system disorders: dizziness, headache, irritability, anxiety, restlessness, agitation, sleep disorders, insomnia, tremor, confusion/fainting, delirium, convulsions, hallucinations, presyncopal state, acute encephalopathy.

Cardiovascular system disorders: palpitations, tachycardia, decreased blood pressure, arrhythmias, cardialgia, increased frequency of angina attacks, extrasystole (ventricular, supraventricular), heart failure.

Blood and lymphatic system disorders: red blood cell aplasia.

Immune system disorders: hypersensitivity reactions, including angioedema, anaphylactic and anaphylactoid reactions, bronchospasm.

Skin and subcutaneous tissue disorders: skin rashes, exfoliative dermatitis, pruritus, urticaria.

General disorders: fever, weakness, feeling hot and hyperemia of face, hyperhidrosis, shortness of breath.

Laboratory parameters: electrolyte imbalance, acid-base balance disorders and increased blood levels of creatinine.

In most of cases, side effects disappeared after reducing the dose of the drug.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Shelf life: 2 years.

Special precautions for storage.

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

Keep out of reach of children.

Nature and contents of container.

10 tablets in a blister; 5 blister packages in carton box.

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 last revision.

06.03.2020.

