APPROVED
The Order of Ministry of Health of Ukraine
_12.04.2024 № _620
Registration certificate
№ UA/20432/02/01

INSTRUCTION
for medical use

PANKALOR®

Composition:
active substance: acetylcysteine;
1 sachet (1 g of granules) contains acetylcysteine 200 mg;
excipients: sorbitol (E 420), aspartame (E 951), orange flavouring.

Pharmaceutical form. Granules for oral solution.
Basic physicochemical properties: White to off white granules with characteristics orange odour.

Pharmacotherapeutic group. Medicines used for coughs and colds. Mucolytic agents. ATC-code: R05C B01.

Pharmacological properties.
Pharmacodynamics.
N-acetyl-L-cysteine (AC) exerts an intense mucolytic-fluidizing action on mucous and mucopurulent secretions by depolymerizing the mucoproteic complexes and the nucleic acids which confer viscosity to the vitreous and purulent component of the sputum and other secretions. Additional properties: reduction of induced mucocyte hyperplasia, increase in surfactant production due to stimulation of type II pneumocytes, stimulation of the activity of the mucociliary apparatus, which contributes to the improvement of mucociliary clearance.
Acetylcysteine also exerts a direct antioxidant action, having a free thiol (SH) nucleophilic group that is able to interact directly with electrophilic groups of oxidant radicals. Of particular interest is the recent finding that acetylcysteine protects α1-antitrypsin enzyme inhibiting elastase from inactivation by hypochlorous acid (HOCl), a powerful oxidant agent produced by the myeloperoxidase enzyme of activated phagocytes.
Due to its molecular structure, acetylcysteine can readily cross cell membranes. Inside the cell, AC is deacetylated to L-cysteine, an amino acid essential for glutathione synthesis. In addition to this, AC, which is a precursor of glutathione, has an indirect antioxidant effect. Glutathione is a highly reactive tripeptide found ubiquitously in the various tissues of animals and is essential for the maintenance of functional capacity as well as cellular morphological integrity. It is the most important protective intracellular mechanism against oxidant radicals, both exogenous and endogenous, as well as toward numerous cytotoxic substances, including paracetamol.
Paracetamol has a cytotoxic effect by progressively reducing the content of glutathione. AC plays a primary role in maintaining adequate levels of glutathione, thus enhancing cellular defences. As a result, AC is a specific antidote for paracetamol poisoning.

In patients with chronic obstructive pulmonary disease, taking 1200 mg AC per day for 6 weeks led to a significant increase in inspired volume and FVC (forced vital capacity of the lungs), possibly due to a decrease in air intake.
In patients with idiopathic pulmonary fibrosis (IPF), the use of oral acetylcysteine 600 mg 3 times daily for one year in combination with standard IPF therapy (prednisone and azathioprine) contributed to the preservation of vital lung capacity (VLC) and lung diffusing capacity, measured by the method of carbon monoxide single-breath.
In the form of inhalation therapy for one year, AC helped reduce the intensity of disease progression in patients with IPF.
When used in very high doses (up to 3000 mg daily for 4 weeks), AC did not have a significant toxic effect on patients with cystic fibrosis.
The antioxidant efficacy of AC is associated with a pronounced decrease in elastase activity in sputum, which is the most significant indicator of lung function in patients with cystic fibrosis. In addition, against the background of treatment, a decrease in the number of neutrophils in the respiratory tract, as well as the number of neutrophils actively secreting elastase-rich granules, was noted.
Pharmacokinetics.
Absorption.
Following oral administration, acetylcysteine is completely absorbed in humans. Due to metabolism in the intestinal wall and the first-pass effect, the oral bioavailability of acetylcysteine is very low (approximately 10%). No differences were found for different dosage forms. In patients with various respiratory and heart diseases, the maximum concentration of AC in the blood plasma is reached 1–3 hours after administration and remains high for 24 hours.
Distribution.
Acetylcysteine is distributed in the body both in unchanged form (20%) and in the form of metabolites (active) (80%), while it is mainly found in the liver, kidneys, lungs and bronchial secretions. The distribution volume of AC is from 0.33 to 0.47 l/kg. Binding to blood plasma proteins is about 50% 4 hours after administration and decreases to 20% after 12 hours.
Biotransformation.
After oral administration, AC is quickly and extensively metabolized in the walls of the intestine and liver. The formed metabolite, cysteine, is considered active. Further, acetylcysteine and cysteine are metabolized in the same way.
Elimination.
About 30% of the dose is excreted by the kidneys. After ingestion, the half-life ($T_{1/2}$) of AC is 6.25 (4.59–10.6) hours.

Clinical characteristics.
***Indications*.**
- Treatment of acute and chronic diseases of the bronchopulmonary system, accompanied by increased production of viscous sputum.
- Paracetamol overdose.

Contraindications.
- Hypersensitivity to acetylcysteine or any of the excipients.
- Ulcer disease of the stomach and duodenum in the stage of exacerbation, haemoptysis, pulmonary bleeding.
- Phenylketonuria (see section “Special warnings and precautions for use”).
- Children under 2 years of age. However, this is not a contraindication for use in the treatment of paracetamol overdose.

***Interactions with other medicinal products and other forms of interaction*.**
Interaction studies were conducted only with the participation of adult patients.

The use of antitussives together with acetylcysteine can increase sputum stagnation due to suppression of the cough reflex.
If the simultaneous use of acetylcysteine with oral antibiotics is necessary, an interval of 2 hours should be observed between the use of these drugs. This does not apply to loracarbef.
Concomitant use of acetylcysteine and nitroglycerin can cause significant arterial hypotension and short-term increase in arterial dilatation. If the simultaneous use of nitroglycerin and acetylcysteine is necessary, patients should be observed for signs of arterial hypotension and warned of the possible occurrence of headache.
Concomitant use of acetylcysteine and carbamazepine may lead to subtherapeutic levels of carbamazepine.
Activated charcoal in high doses (as an antidote) may reduce the effect of acetylcysteine.
Effect on laboratory investigations.
Acetylcysteine can affect the colorimetric study of salicylates and the determination of ketone bodies in urine.

Special warnings and precautions for use.
Patients suffering from bronchial asthma should be under strict supervision during treatment due to the possible development of bronchospasm. In case of bronchospasm, treatment with acetylcysteine should be discontinued immediately.
Mucolytic agents can cause bronchial obstruction in children under 2 years of age. As a result of the physiological features of the respiratory system in children of this age group, the ability to clean the secretions of the respiratory tract is limited. Therefore, mucolytic agents should not be used in children under 2 years of age (see section “Contraindications”).
It is necessary to use the drug with caution in case of a tendency to gastrointestinal bleeding (varicose veins of the oesophagus, peptic ulcer), since oral intake of acetylcysteine can cause vomiting.
It is recommended to take the drug with caution in patients with a history of gastric and duodenal ulcers, especially in the case of concomitant use of other drugs that irritate the gastric mucosa.
Acetylcysteine should be administered with caution to patients with liver or kidney disease to avoid accumulation of nitrogen-containing substances in the body.
Severe skin reactions, such as Stevens-Johnson syndrome and Lyell’s syndrome, have been reported very rarely in association with the use of acetylcysteine. If new skin and mucous membrane changes appear, treatment with acetylcysteine should be discontinued immediately.
Acetylcysteine affects the metabolism of histamine, so long-term therapy should not be prescribed to patients with histamine intolerance, as this may lead to the appearance of symptoms of intolerance (headache, vasomotor rhinitis, itching).
The use of acetylcysteine, mainly at the beginning of treatment, can cause thinning of the bronchial secretion and increase its volume. If the patient is unable to effectively cough up sputum, postural drainage and bronchoaspiration should be performed.

Excipients.
The drug contains aspartame, which is a derivative of phenylalanine, which is dangerous for patients with phenylketonuria (see the section “Contraindications”).

Effects on the ability to drive and use machines.
Pregnancy.
Clinical data on the use of acetylcysteine in pregnant women are limited. Animal studies have not revealed direct or indirect adverse effects on reproductive toxicity.
Pankalor®, granules for oral solution, should be avoided during pregnancy.
Before using the drug during pregnancy, the potential risks and expected benefits should be considered.
Breast-feeding.

There is no information on the excretion of acetylcysteine and/or its metabolites into breast milk. A risk to the infant cannot be excluded.
It is necessary to make a decision on the termination of breastfeeding or on the termination/refusal of the use of the drug Pankalor®, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Fertility.
There are no data on the effect of acetylcysteine on human fertility. Animal studies have not revealed harmful effects on human fertility when using the drug in recommended doses.

Effects on the ability to drive and use machines.
There is no confirmation that acetylcysteine affects the ability to drive a car and other mechanisms. However, patients should be informed that due to rare adverse effects such as drowsiness or nausea, acetylcysteine may reduce their alertness and ability to drive and operate machinery.

Administration and dosage.
The drug is intended for oral administration.
Dissolve the contents of the sachet while stirring in 1/2 cup of water and drink as soon as possible. Apply before meals.
The drug should not be taken for more than 4–5 days without consulting a doctor. Additional fluid intake increases the mucolytic effect of the drug.
Treatment of acute and chronic diseases of the bronchopulmonary system accompanied by increased production of sputum.
Adults and children aged 14 and over.
200 mg 2 or 3 times a day.
Children of 6–14 years old.
200 mg 2 times a day.
Children of 2–6 years old.
100 mg (half of the solution obtained after dissolving one sachet) 2–3 times a day.
Impaired renal/hepatic function.
No dose adjustment is required for patients with mild to moderate renal/hepatic insufficiency.
For patients with severe renal/hepatic impairment, the daily dose or interval between doses should be reduced.

Paracetamol overdose.
In the first 10 hours after taking a toxic substance, it is necessary to take Pankalor® in the dose of 140 mg/kg as soon as possible, then in the dose of 70 mg/kg every 4 hours for 1–3 days.

Children.
It may be administered to children aged 2 years and older.

Overdose.
There are no data on cases of overdose of medicinal forms of acetylcysteine intended for oral administration.
Volunteers took 11.2 g of acetylcysteine per day for three months without any serious adverse effects.
Acetylcysteine when used in a dose of 500 mg/kg/day does not cause an overdose.
Symptoms.
Overdose may be manifested by gastrointestinal symptoms such as nausea, vomiting and diarrhoea.
Treatment.
There is no specific antidote for acetylcysteine poisoning, the therapy is symptomatic.

Adverse reactions.
The most common adverse reactions associated with oral acetylcysteine are gastrointestinal reactions.
Adverse reactions, information about which is given below, are classified by organ system and frequency of occurrence. The frequency category of adverse reactions is defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000) and unknown (cannot be estimated from available data).
In each group, adverse reactions are presented in order of decreasing severity.
Immune system disorder: uncommon – hypersensitivity; rare – skin allergic reactions; very rare – anaphylactic/anaphylactoid reactions, anaphylactic shock.
Nervous system disorders: uncommon – headache; very rare – somnolence.
Ear and labyrinth disorders*:* uncommon – tinnitus.
Cardiac disorders: uncommon – tachycardia.
Vascular disorders: very rare – haemorrhages (bleeding).
Blood and lymphatic system disorders: frequency unknown – anaemia, decreased platelet aggregation, but the clinical significance of this has not been determined.
Respiratory, thoracic and mediastinal disorders: uncommon – rhinorrhoea; rare – cough, bronchospasm, dyspnoea, shortness of breath.
Gastrointestinal disorders: uncommon – stomatitis, abdominal pain, nausea, vomiting, diarrhoea; rare – dyspepsia; frequency unknown – stomatitis, abdominal pain, nausea, vomiting, diarrhoea; rare – dyspepsia; frequency unknown – bad breath.
Skin and subcutaneous tissue disorders: uncommon – itching, urticaria, erythema, rash, angioedema; very rare – Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome); frequency unknown – eczema.
General disorders and administration site conditions: uncommon – hyperthermia; frequency unknown – facial swelling.
Effect on the results of laboratory and instrumental investigations: uncommon – decreased arterial pressure.
Episodes of decreased platelet aggregation were observed, but no clinical significance was determined.
Reported suspected adverse reactions.
The reporting of adverse reactions after the registration of the medicinal product is of great importance. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua.

Shelf-life. 2 years.

Storage conditions.
Store at a temperature not exceeding 25 °C in the original packaging.
Keep out of the reach of children.

Incompatibility.
When dissolving acetylcysteine, it is necessary to use glassware, avoid contact with metal and rubber surfaces.
It is not recommended to dissolve acetylcysteine with other drugs in one glass.

Package.

1 g of granules in a sachet. 10 or 30 sachets in a carton package.

Conditions of supply.
Without prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

Date of last revision. 12.04.2024