**APPROVED**
**The Order of Ministry of**
**Health of Ukraine**
**15.07.2021 № 1452**
**Registration certificate**
**№ UA/9928/04/01**

# INSTRUCTION
## for medical use

## ABROL®

***Composition:***
*active substance:* ambroxol hydrochloride;
2 ml of solution for inhalation and oral administration contain ambroxol hydrochloride 15 mg;
*excipients:* citric acid, monohydrate; sodium chloride; benzalkonium chloride solution; sodium hydrogen phosphate, dihydrate; purified water.

**Pharmaceutical form.** Solution for inhalation and oral administration.
*Basic physico-chemical properties:* clear, colourless or slightly brownish solution with a characteristic odor.

**Pharmacotherapeutic group.**
Drugs used in cough and catarrhal diseases. Mucolytics.
ATC code R05C B06.

***Pharmacological properties.***
*Pharmacodynamics.*
The active substance of the solution for inhalation and oral administration Abrol® – ambroxol hydrochloride – is a substituted benzylamine which is a metabolite of bromhexine. It differs from bromhexine by the absence of a methyl group and the presence of a hydroxyl group in the para-trans-position of the cyclohexyl ring.
Investigations prove its secretolytic and secretomotor effects in the bronchial tract.
Following oral administration, the effect commences after 30 minutes on average and persists for 6–12 hours depending on the individual dose.
In preclinical investigations, ambroxol hydrochloride has been proved to increase the proportion of serous bronchial secretion. Ambroxol promotes the transport of mucus by reducing viscosity and activating the ciliated epithelium.
Ambroxol induces the activation of the surfactant system by acting directly on the type II pneumocytes of the alveoles and the Clara cells in the region of the small airways. It promotes the formation and outward transfer of surface-active material in the alveolar and bronchial tree of the fetal and adult lungs. These effects have been demonstrated in cell cultures and *in vivo* on various species.
Moreover, ambroxol demonstrated anti-oxidant effects in numerous pre-clinical investigations.
*Pharmacokinetics.*
*Absorption.* Ambroxol is almost completely absorbed following oral use. $T_{max}$ following oral use is 1–3 hours. Absolute bioavailability of ambroxol upon oral administration decreases by approximately 1/3 as a result of first-pass metabolism.
*Distribution.* Approximately 85 % (80–90 %) of the drug binds to plasma proteins. Ambroxol reaches a higher concentration in lung tissues than in blood plasma upon parenteral administration. Ambroxol passes into the cerebrospinal fluid, crosses the placental barrier and can also be found in breast milk.
*Metabolism.* Metabolites subject to renal excretion (e.g. dibromanthranilic acid, glucuronide) are formed in the liver.

*Excretion.* Nearly 90 % of the drug is excreted through the kidneys in the form of metabolites formed in the liver. Less than 10 % of ambroxol is excreted unchanged through the kidneys. Due to the high protein binding, high volume of distribution and slow redistribution from the tissue to the blood, major elimination of ambroxol through dialysis or forced diuresis is unlikely.
The terminal half-life in the plasma is 7–12 hours. The plasma half-life of ambroxol and its metabolites is approximately 22 hours.
*Patients with impaired hepatic and renal function.* Clearance of ambroxol is reduced by 20–40 % in patients with severe hepatic diseases. Accumulation of the metabolites of ambroxol can occur in patients with severe renal dysfunction.

**Clinical characteristics.**
***Indications.***
Secretolytic therapy in acute and chronic bronchopulmonary diseases associated with impaired secretion of bronchial mucus and decreased mucus transport.

***Contraindications.***
Abrol®, solution for inhalation and oral administration, should not be used in patients with hypersensitivity to ambroxol hydrochloride or to any excipients of the drug.

***Interaction with other medicinal products and other forms of interaction.***
Concomitant use of Abrol® and cough-suppressants may lead to excessive accumulation of mucus due to inhibition of the cough reflex. Therefore, this combination is possible only after careful evaluation of the ratio of the expected benefit and possible risk of the use by the doctor.
Concomitant administration of ambroxol and antibiotics (amoxicillin, cefuroxime, doxycycline and erythromycin) results in increased antibiotic concentrations in the bronchopulmonary secretion and sputum.

***Administration details.***
Abrol®, solution for inhalation and oral administration, contains benzalkonium chloride solution as a preservative. When inhaled, benzalkonium chloride can cause bronchospasm.
There have been reports of severe skin reactions: erythema multiforme, Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol hydrochloride. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, ambroxol hydrochloride treatment should be discontinued immediately and medical advice should be sought.
In case of impaired bronchial motility and increased mucus secretion (e.g. in rare cases of primary ciliary dyskinesia), Abrol®, solution for inhalation and oral administration, should be used with caution due to the risk of potential mucus accumulation.
Patients with impaired renal function or severe hepatic failure should take Abrol®, solution for inhalation and oral administration, only after consulting their physician. The accumulation of metabolites formed in the liver may occur in patients with severe renal failure when using ambroxol, as well as any other active substance metabolized in the liver and excreted by the kidneys.
Abrol®, solution for inhalation and oral administration, contains 49.8 mg of sodium in the recommended daily dose. Patients following a sodium-controlled diet should keep this in mind.

*Use during pregnancy or breast feeding*
*Pregnancy.*
Ambroxol hydrochloride crosses the placental barrier. As a result of clinical trials of the drug after the 28$^{th}$ week of gestation, no harmful effects on the fetus have been revealed. Animal studies have revealed no direct or indirect adverse effects on the course of pregnancy, development of the embryo/fetus, childbirth or postnatal development. However, it is necessary to follow usual precautions regarding taking medications during pregnancy. Especially during the I trimester, it is not recommended to use Abrol®.

*Breast feeding.*
Ambroxol hydrochloride penetrates into the breast milk. Abrol® is not recommended for use during breast feeding.
*Fertility.*
Preclinical studies do not indicate direct or indirect adverse effects on fertility.

*Effect on reaction rate when driving motor transport or using other mechanisms.*
There is no evidence for an effect on reaction rate when driving motor transport or working with other mechanisms. Studies of the effect on reaction rate when driving motor transport or working with other mechanisms have not been conducted.

***Dosage and administration.***
*Inhalation Solution*
*Adults and children from 6 years of age:* 1–2 inhalations of 2–3 ml of solution per day.
*Children under 6 years of age:* 1–2 inhalations of 2 ml of solution per day.
Abrol®, inhalation solution, may be used in all modern inhaler devices (except for the steam inhalers).
Abrol®, inhalation solution, should be diluted in a proportion 1:1 with physiological solution to ensure optimal humidification of air released by the device.
Abrol®, inhalation solution, should not be mixed with cromoglycic acid. It should also not be mixed with other solutions, in a mixture with which the pH of the solution exceeds 6.3, for example, with alkaline inhalation salt (*Emser Salt*). Increasing the pH of the solution can increase precipitation of the free base of ambroxol hydrochloride or cause opalescence of the solution.
Before inhalation it is usually recommended to heat the inhalation solution to body temperature.
If only one inhalation per day is possible, Abrol® for oral use should be administered additionally.
Considering that the process of inhalation itself may provoke coughing, patients are advised to breathe normally during inhalation.
Prior to inhalation, patients with bronchial asthma should use bronchodilators to open up the lungs.
*Oral solution.*
*Adults and adolescents from 12 years of age:* 4 ml 3 times daily during the first 2–3 days, which is equivalent to 90 mg of ambroxol per day, then 2 ml 3 times daily, which is equivalent to 45 ml of ambroxol per day. The 4 ml 3 times daily dosage may be continued after consulting the physician.
*Children aged 6 to 12 years:* 2 ml 2–3 times daily, which is equivalent to 30–45 mg of ambroxol per day.
*Children aged 2 to 6 years:* 1 ml 3 times daily, which is equivalent to 22,5 mg of ambroxol per day.
*Children under 2 years of age:* 1 ml 2 times daily, which is equivalent to 15 mg of ambroxol per day.
*Dosage in patients with renal and/or hepatic impairment.*
In severe renal or hepatic impairment, the drug should only be administered following medical consultation as it may be required to reduce the maintenance dose or prolong the interval between drug administrations.
Abrol®, inhalation and oral solution, should not be used longer than 4–5 days without consulting a physician.
In acute conditions, if symptoms worsen or do not improve despite the administration of Abrol®, it is recommended to consult a physician.
Abrol®, oral solution, can be diluted in water, tea, juice or milk. Abrol® can be taken with or without food.
The secretolytic effect of Abrol® is supported by adequate fluid intake.

*Children.*
The drug can be used in pediatric practice. The drug can be used in children under 2 years of age by medical prescription only.

***Overdose.***
At present there are no reports on specific symptoms of overdose. Symptoms known from isolated reports on overdose and/or cases of using drugs by mistake correspond to the known adverse reactions of ambroxol hydrochloride in the recommended doses and require symptomatic treatment.

***Adverse reactions.***

Adverse reactions divided per System Organ Class and frequency are as follows:
very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000, including isolated cases), not known (frequency cannot be estimated from the available data).
*Immune system disorders:* rare – hypersensitivity reactions; not known – anaphylactic reactions including anaphylactic shock, angioedema and pruritus.
*Skin and subcutaneous tissue disorders:* rare – rash, urticaria; not known – severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).
*Nervous system disorders:* common – dysgeusia (changed taste).
*Gastrointestinal disorders:* common – nausea, decreased sensitivity in the mouth; uncommon –vomiting, diarrhea, dyspepsia, abdominal pain, dry mouth; rare – dry throat; very rare – salivation.
*Respiratory, thoracic and mediastinal disorders:* common – pharyngeal hypoesthesia; very rare – dyspnea and bronchospasm; not known – dyspnea (as a symptom of a hypersensitivity reaction),
*General disorders:* uncommon – fever, reactions in mucous membranes.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to continue monitoring the correlation of the benefits and risks related to the use of this medicinal product. Healthcare professionals must report all suspected adverse reactions to the State Enterprise "State Expert Center of the Ministry of Health of Ukraine" and to the applicant through the feedback form at the website: https://kusum.ua/pharmacovigilance/

***Shelf life.***
2 years.

**Storage conditions.**
Store at a temperature not more than 25 °C.
Keep out of reach of children.

**Package.**
100 ml are in a glass bottle with a tamper evident cap; 100 ml are in a glass bottle with a child proof cap. Each bottle is in a carton box with a 5 ml syringe dispenser and syringe adaptor.

**Conditions of supply.**
Without prescription.

**Manufacturer.**
"KUSUM PHARM" LLC.

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

**Date of last revision.**
15.07.2021 № 1452