APPROVED
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INSTRUCTION
for medical use

ABROL®

Composition:
active substance: ambroxol hydrochloride;
2 ml of solution for inhalation and oral administration contains 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, colorless 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 component of 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 in the alveoli and the Clara cells in 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* in various species.
Moreover, ambroxol demonstrated anti-oxidant effects in numerous preclinical investigations.
The use of ambroxol hydrochloride is followed by an increase in the concentration of antibiotics (amoxicillin, cefuroxime, erythromycin, and doxycycline) in bronchopulmonary secretions and in the sputum. As of now, the clinical significance of this fact has not been determined.
Antiviral properties in vitro and in experimental animal models
In *in vitro* studies, a decrease in rhinovirus (RV 14) replication on human tracheal epithelial cells was observed. In a mouse respiratory model, a decrease in influenza A virus replication was observed after pretreatment with ambroxol. To date, the clinical significance of this effect has not been confirmed.

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 be found in breast milk.
Metabolism. Metabolites subject to renal excretion (e.g. dibromanthranilic acid, glucuronide) are formed in the liver.
Elimination. 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 by the kidneys. Due to the high protein binding, high volume of distribution and slow redistribution from the tissues to the blood, major elimination of ambroxol through dialysis or forced diuresis is unlikely.
The terminal plasma half-life 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 other ingredients of the drug.

Interaction with other medicinal products and other forms of interaction.
When Abrol® is used in combination with cough suppressants in patients with respiratory diseases associated with hypersecretion of mucus, such as cystic fibrosis or bronchiectasis, (dangerous) accumulation of secretions due to suppression of the cough reflex may occur.

Administration details.
Since all inhalation drugs can cause bronchospasm, the medicinal product Abrol should not be used in patients with known bronchial hyperreactivity and/or with detected atopy.
There have been reports of severe skin reactions: erythema multiforme, Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) associated with the administration of ambroxol hydrochloride. If 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® only after consulting their physician. In patients with severe renal failure, the use of ambroxol, as well as any other active substance metabolized in the liver and then excreted by the kidneys, may be associated with accumulation of metabolites formed in the liver.
Excipients.
Abrol®, solution for inhalation and oral administration, contains benzalkonium chloride solution as a preservative. When inhaled, benzalkonium chloride can cause bronchospasm.
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 breastfeeding.
Pregnancy.
Ambroxol hydrochloride crosses the placental barrier. As a result of clinical trials of the drug after the 28th week of gestation, no harmful effects on the fetus and course of pregnancy have been revealed. Preclinical studies have revealed no direct or indirect adverse effects on the course of pregnancy, embryonic/fetal development, childbirth or postnatal development. However, it is necessary to follow the usual precautions regarding the administration medications during pregnancy. Especially during the I trimester, it is not recommended to use Abrol®.
Breastfeeding.
Ambroxol hydrochloride is excreted into breast milk. Abrol® is not recommended for use during breastfeeding.
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 of the effect on the reaction rate when driving motor transport or using other mechanisms. Studies of the effect on reaction rate when driving motor transport or using other mechanisms have not been conducted.

Dosage and administration.
Solution for inhalation
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®, solution for inhalation, may be used in all modern inhaler devices (except for the steam inhalers).
Abrol®, solution for inhalation, should be diluted in a 1:1 ratio with physiological saline solution to ensure optimal humidification of air released by the device.
Abrol®, solution for inhalation, should not be mixed with cromoglicic 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 clouding of the solution.
Before inhalation it is usually recommended to warm 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®, solution for inhalation and oral administration, 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 regardless of food intake.
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 regarding the specific symptoms of overdose. Symptoms known from isolated reports on overdose and/or cases of using the drug by mistake correspond to the known adverse reactions of ambroxol hydrochloride in the recommended doses and require symptomatic treatment.

Adverse reactions.
Adverse reactions by organ systems and frequency are listed below:
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), frequency unknown (frequency cannot be estimated from the available data).
In each group the adverse reactions are listed in order of decreasing severity.
Immune system disorders: rare – hypersensitivity reactions; frequency unknown – anaphylactic reactions including anaphylactic shock, angioedema, pruritus.
Skin and subcutaneous tissue disorders: rare – rash, urticaria; frequency unknown – severe cutaneous adverse reactions (including erythema multiforme, Stevens–Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).
Nervous system disorders: common – dysgeusia (taste disorder).
Gastrointestinal disorders: common – nausea, oral hypoesthesia; 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; frequency unknown – dyspnea (as a symptom of a hypersensitivity reaction).
General disorders: uncommon – fever, mucosal reactions.
Reporting of suspected adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf life.
3 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.
LLC “KUSUM PHARM”.

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

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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