APPROVED
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Health of Ukraine
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INSTRUCTION
for medical use

ABROL®

Composition:
active substance: ambroxol hydrochloride;
1 tablet contains 30 mg ambroxol hydrochloride;
excipients: silica colloidal anhydrous, croscarmellose sodium, microcrystalline cellulose, magnesium stearate.

Pharmaceutical form. Tablets.
Basic physico-chemical properties: round white tablets with a score line on one side.

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

Pharmacological properties.
Pharmacodynamics.
Ambroxol hydrochloride is a substituted benzylamine and a metabolite of bromhexine. Ambroxol hydrochloride is proved to increase serous bronchial secretion and pulmonary surfactant production by direct effect on the type II pneumocyte in alveoli and Clara cells in bronchioles. Ambroxol hydrochloride also stimulates the ciliary activity, which results in reduced sputum viscosity and its improved expulsion (mucociliary clearance). Improved mucociliary clearance has been proven in clinical and pharmacological studies.
Enhanced serous secretion and enhanced mucociliary clearance facilitate expectoration and ease cough.
In patients with COPD, long-term treatment (6 months) with ambroxol hydrochloride (in the 75 mg oral sustained release form) resulted in significant reduction of exacerbations after two months of treatment. In patients receiving ambroxol hydrochloride, the duration of treatment and antibiotic therapy was significantly shorter. Compared to placebo, treatment with ambroxol hydrochloride in the oral sustained release form showed a statistically significant improvement of symptoms associated with difficulty with expectoration, cough, dyspnea and auscultatory findings.
Local anesthetic effect of ambroxol hydrochloride, which can be attributed to sodium channel blocking properties, was observed in the rabbit eye model.
In vitro studies have shown that ambroxol hydrochloride blocks neuronal sodium channels; binding was reversible and concentration-dependent.
Ambroxol hydrochloride showed an anti-inflammatory effect *in vitro*. Therefore, ambroxol hydrochloride significantly reduces cytokine release from the mononuclear and polymorphonuclear blood and tissue cells.

Clinical trials involving patients with pharyngitis have demonstrated a significant decrease in pain and redness in the throat with the drug.
Due to the pharmacological properties of ambroxol, pain was rapidly alleviated during treatment of upper respiratory tract diseases, which was observed during studies of the clinical efficacy of inhaled forms of ambroxol.
The use of ambroxol hydrochloride increases the concentration of antibiotics (amoxicillin, cefuroxime, erythromycin, and doxycycline) in bronchopulmonary secretions and in the sputum. As of now, no clinical significance of this fact has 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 airway model, reduction of influenza A virus replication was observed after pretreatment with ambroxol.
As of now, the clinical significance of this fact has not been confirmed.
Pharmacokinetics.
Absorption. Absorption of ambroxol hydrochloride from oral immediate-release forms is fast and complete, with a linear dependence on the dose in the therapeutic range. Maximum plasma levels are reached within 1-2,5 hours upon oral administration of rapid release dosage forms and on average in 6,5 hours upon administration of sustained-release dosage forms.
The absolute bioavailability after administration of a 30 mg tablet is 79%.
Distribution. Upon oral administration, the distribution of ambroxol hydrochloride from the blood to the tissues is rapid and pronounced, with the highest concentration of the active substance achieved in the lungs. The estimated volume of distribution upon oral administration is 552 l. Approximately 90 % of the drug is bound to plasma proteins in the therapeutic range.
Metabolism and elimination. About 30 % of an orally administered dose is eliminated via first pass metabolism. Ambroxol hydrochloride is metabolized primarily in the liver by glucuronidation and decomposition to dibromanthranilic acid (approximately 10 % of the dose). The metabolism of ambroxol hydrochloride to dibromanthranilic acid occurs with CYP3A4. Within 3 days of oral administration, approximately 6 % of the dose is excreted unchanged in the urine, approximately 26 % of the dose is excreted in a conjugated form.
The plasma elimination half-life is approximately 10 hours. The total clearance is in the range of 660 ml/min. The renal clearance is about 8 % of the total clearance. After 5 days, approximately 83% of the total dose is excreted in the urine.
Pharmacokinetics in special groups of patients. In patients with hepatic impairment, excretion of ambroxol hydrochloride is reduced, resulting in 1,3-2-fold higher plasma levels. As the therapeutic range of ambroxol hydrochloride is wide enough, dose adjustment is not required.
Age and sex have no clinically significant effect on the pharmacokinetics of ambroxol hydrochloride, so no dose adjustment is required.
Food intake does not affect the bioavailability of ambroxol hydrochloride.

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

Contraindications.
Abrol®, tablets should not be used in patients with known hypersensitivity to ambroxol hydrochloride or to other components of the drug.
Abrol®, tablets is not intended for use in children under 6 years. Ambroxol in the appropriate dosage is recommended for use in children under 6 years.

Interaction with other medicinal products and other forms of interaction.

The concomitant use of the drug Ambroxol, 30 mg tablets and antitussives in patients with existing respiratory diseases associated with mucus hypersecretion, such as cystic fibrosis or bronchiectasis, may cause (dangerous) mucus accumulation due to inhibition of the cough reflex.

Administration details.
There have been reports of severe skin lesions such as erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) associated with the use of ambroxol hydrochloride. If there are symptoms or signs of progressive skin rash (sometimes associated with blisters or mucosal lesions), treatment with ambroxol hydrochloride should be discontinued immediately and medical advice should be sought.
In case of impaired bronchial motility and increased mucus secretion (e.g., rare cases of primary ciliary dyskinesia) the drug Abrol® should be used with caution due to the risk of potential mucus accumulation.
Patients with impaired renal function or severe hepatic failure should use the drug Abrol®, tablets, only after consulting a physician. The use of ambroxol hydrochloride or any other active substance metabolized in the liver and then excreted by the kidneys, is associated with the accumulation of metabolites formed in the liver of patients with severe renal failure.
Excipients.
This medicinal product contains 0.0065 mmol of sodium (or 0.15 mg) per tablet, therefore, it is essentially sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy. Ambroxol hydrochloride crosses the placental barrier. Preclinical studies have revealed no direct or indirect adverse effects on the course of pregnancy, embryonic/fetal development, childbirth or postnatal development.
The results of clinical trials regarding the use of ambroxol hydrochloride after the 28th week of gestation have revealed no adverse effects on the fetus. However, the usual precautions regarding the use of drugs during pregnancy should be followed. Especially during the I trimester of pregnancy, the use of the drug Abrol®, tablets is not recommended.
Breastfeeding. Ambroxol hydrochloride is excreted into breast milk. The drug Abrol®, tablets is not recommended for use during breastfeeding.
Fertility. Preclinical studies do not indicate direct or indirect adverse effects of ambroxol hydrochloride on fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.
There is no data concerning the effect on the reaction rate when driving motor transport or using other mechanisms. The effect on the reaction rate when driving motor transport or using other mechanisms has not been studied.

Dosage and administration.
Unless otherwise specified it is recommended to administer the drug Abrol®, tablets, as follows:
children from 6 to 12 years of age: the usual dose is $^1/_2$ of a tablet 2-3 times daily (equivalent to 30-45 mg ambroxol hydrochloride a day);
adults and children over 12 years of age: the usual dose is 1 tablet 3 times daily during the first 2-3 days (equivalent to 90 mg ambroxol hydrochloride a day). Treatment should be continued by using 1 tablet 2 times daily (equivalent to 60 mg ambroxol hydrochloride a day).
If necessary, the therapeutic effect for adults and children over 12 years of age may be enhanced by using 2 tablets 2 times daily (equivalent to 120 mg ambroxol hydrochloride a day).
Tablets should be swallowed whole with a sufficient amount of liquid (e.g., water, tea or fruit juice) with or without food.

In general, there are no restrictions regarding the duration of use, but prolonged therapy should be conducted under medical supervision.
Abrol® tablets should not be used for longer than 4-5 days without consulting a physician.

Children.
The drug should be used in children over 6 years of age who are intolerant to syrup or solution for inhalation and oral use.

Overdose.
Cases of overdose have not been reported to date. Symptoms known from isolated reports on overdose and/or cases of using the drug by mistake are consistent with known adverse reactions of ambroxol hydrochloride in the recommended doses and require symptomatic treatment.

Adverse reactions.
Adverse reactions are listed below according to organ systems and frequency:
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 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 (Lyell's syndrome), acute generalized exanthematous pustulosis).
Nervous system disorders: frequency unknown – dysgeusia (taste disorder).
Gastrointestinal disorders: common – nausea; uncommon – vomiting, diarrhea, dyspepsia, abdominal pain; very rare – salivation; frequency unknown – oral hypoesthesia, dry mouth, dry throat, heartburn, constipation.
Respiratory, thoracic and mediastinal disorders: frequency unknown – dyspnea (as a symptom of a hypersensitivity reaction), rhinorrhea, respiratory tract dryness, pharyngeal hypoesthesia, dyspnea and bronchospasm.
Urinary disorders: frequency unknown – dysuria.
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 in the original package at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
10 tablets are in a blister; 2 blisters are in a carton box.

Conditions of supply.

Without prescription.

Manufacturer.
LLC “KUSUM PHARM”.
or
KUSUM HEALTHCARE PVT LTD.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.
or
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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