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INSTRUCTION
for medical use

ABROL® SR

Composition:
active substance: ambroxol hydrochloride;
each sustained release capsule contains: ambroxol hydrochloride 75 mg;
excipients: microcrystalline cellulose, xanthan gum, hypromellose, hydroxypropyl cellulose, magnesium stearate, hard gelatin capsule*;
*hard gelatin capsule: gelatin, purified water, titanium dioxide (E 171).

Pharmaceutical form. Sustained release capsules.
Main physical and chemical properties: non-transparent capsules with a creamy white body and a creamy white cap, containing a white powder.

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

Pharmacological properties.
Pharmacodynamics.
The active substance of the sustained release capsules Abrol®SR – ambroxol hydrochloride – increases the proportion of the serous component of bronchial secretion. Abroxol increases the secretion of lung surfactant through direct effect on type II pneumocytes in the alveoli and Clara cells in bronchioles, as well as stimulates ciliary epithelium activity, resulting in reduced viscosity of the mucus and its improved release (mucociliary clearance). Improvement of mucociliary clearance has been proven during clinical and pharmacological research.
Activation of mucus secretion, reduction of mucus viscosity and increased mucociliary clearance facilitate expectoration and ease cough.
Long-term term treatment (6 months) with ambroxol hydrochloride (in the 75 mg oral sustained release form) led to significant reduction in exacerbations after 2 months of treatment in patients with COPD. The duration of the disease and antibiotic therapy was significantly shorter in patients treated with ambroxol hydrochloride. Compared with placebo, treatment with the oral sustained release form of ambroxol hydrochloride led to 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 demonstrated an anti-inflammatory effect *in vitro*. *In vitro* studies found that 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 ambroxol hydrochloride.
Due to the pharmacological properties of ambroxol, pain was rapidly alleviated during the 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 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. Absorption of ambroxol hydrochloride from oral immediate-release forms is fast and almost complete, with a linear dependence on the dose in the therapeutic range. Maximum levels in blood plasma are reached in 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.
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 volume of distribution upon oral administration is 522 l. Approximately 90 % of the drug is bound to plasma proteins in the therapeutic range.
Metabolism and excretion. Approximately 30 % of the dose is excreted through presystemic metabolism following oral administration. Ambroxol hydrochloride is metabolized primarily in the liver through glucuronidation and decomposition to dibromanthranilic acid (approximately 10% of the dose). Studies on human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol hydrochloride to dibromanthranilic acid.
After 3 days of oral use, approximately 6 % of the dose is excreted unchanged with the urine, approximately 26 % of the dose – in a conjugated form.
Plasma half-life is about 10 hours. Total clearance is within 660 ml/min. Renal clearance is about 8 % of the total. 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 times higher levels in blood plasma. As the therapeutic range of ambroxol hydrochloride is wide enough, there is no need to change the dosage.
Age and sex have no clinically significant effect on the pharmacokinetics of ambroxol hydrochloride, so no dose adjustment is required.

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

Contraindications.

Abrol®SR should not be used in patients with known hypersensitivity to ambroxol hydrochloride or to other ingredients of the drug.
Abrol®SR is not intended for use in children under 12 years of age due to the amount of the active substance present in a capsule.

Interaction with other medicinal products and other forms of interaction.
The simultaneous use of Abrol®SR and cough suppressants in patients with respiratory diseases associated with hypersecretion of mucus, such as cystic fibrosis or bronchiectasis, may lead to (dangerous) accumulation of mucus as a result of inhibition of cough reflex.

Administration details.
There have been reports of severe skin lesions: 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 signs or symptoms of skin rash progression (sometimes associated with the appearance of blisters or mucosal lesions), immediately discontinue treatment with ambroxol hydrochloride and seek medical attention.
In case of impaired bronchial motility and increased mucus secretion (e.g., rare cases of primary ciliary dyskinesia), Abrol®SR 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®SR, sustained release tablets, 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.

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.
As a result of clinical trials of ambroxol hydrochloride after the 28th week of gestation, no harmful effects on the fetus have been revealed.
However, it is necessary to follow the usual precautions regarding the administration of medications during pregnancy. In particular, during the I trimester, it is not recommended to use the sustained-release capsules Abrol®SR.
Breastfeeding.
Based on the results of preclinical studies, ambroxol hydrochloride is excreted into breast milk. Abrol®SR 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 of ambroxol 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.
Unless otherwise specified it is recommended to take the drug Abrol®SR as follows:
Adults and adolescents over 12 years of age: 1 capsule once daily (equivalent to 75 mg/day ambroxol hydrochloride) in the morning or in the evening. Abrol®SR can be taken regardless of the meal. Capsules should be swallowed whole, with enough liquid (water, tea, fruit juice).

In general, there are no restrictions regarding the duration of use, but prolonged therapy should be conducted under medical supervision.
Abrol®SR should not be used for longer than 4-5 days without consulting a doctor.
Children.
The drug should not be used in children under 12 years of age due to the amount of active ingredient contained in the capsule. Ambroxol in the form of syrup 15 mg/5 ml or 30 mg/5ml is recommended for use in children under 12 years of age.

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: 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.
Respiratory, thoracic and mediastinal disorders: frequency unknown – dyspnea (as a hypersensitivity reaction), dyspnea and bronchospasm, pharyngeal hypoesthesia.
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.
2 years.

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

Package.
10 capsules are in a blister. 1 or 2 blisters are in a carton package.

Conditions of supply.
Without prescription.

Manufacturer.
LLC “KUSUM PHARM”.

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

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