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**Health of Ukraine**
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# INSTRUCTION
## for medical use

## ABROL®SR

***Composition:***
*active substance:* ambroxol hydrochloride;
1 tablet contains ambroxol hydrochloride 75 mg;
*excipients:* colloidal silicon dioxide anhydrous, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate.

**Pharmaceutical form.** Sustained release tablets.
*Main physico-chemical properties:* round, biconvex white tablets smooth on both sides.

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

***Pharmacological properties.***
*Pharmacodynamics.*
The active substance of the sustained release tablets 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, dyspnoea 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 the cytokine release from the mononuclear and polymorphonuclear blood and tissue cells.

As a result of clinical trials involving patients with pharyngitis, a significant decrease in pain and redness in the throat when using ambroxol hydrochloride has been proven.
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 increases 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.
*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, 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 are bound to proteins in the blood plasma in therapeutic range.
*Metabolism and excretion.* Approximately 30% of the dose after oral administration is excreted through presystemic metabolism. 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.
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.***
Аброл®SR should not be used in patients with known hypersensitivity to ambroxol hydrochloride or to other ingredients of the drug.
Аброл®SR, sustained release tablets 75 mg, is not intended for use in children under 12 years of age due to the amount of the active substance present in a tablet.

***Interaction with other medicinal products and other forms of interaction.***
Concomitant use of Abrol®SR and cough-suppressants may lead to excessive accumulation of mucus due to inhibition of the cough reflex. Therefore such combination is possible only after careful evaluation by the doctor of ratio of the expected benefit and possible risk of the use.

***Administration details.***
There have been reports of severe skin lesions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised 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., 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 degree of hepatic failure should take Abrol®SR, sustained release tablets, only after consulting their physician. When using ambroxol, as well as any other active substance metabolized in the liver and excreted by the kidneys, the accumulation of metabolites which are formed in the liver of patients with severe renal failure, takes place.

*Use during pregnancy or breast feeding*
*Pregnancy.*
Ambroxol hydrochloride crosses the placental barrier. Animal studies have revealed no direct or indirect adverse effects on the course of pregnancy, development of the embryo/fetus, childbirth or postnatal development.
As a result of clinical trials of ambroxol hydrochloride after the 28$^{th}$ week of gestation, no harmful effects on the fetus have been revealed.
However, it is necessary to follow usual precautions regarding taking medications during pregnancy. Especially during the I trimester, it is not recommended to use the tablets Abrol®SR.
*Breast feeding.*
Based on the results of preclinical studies ambroxol hydrochloride penetrates into the breast milk. Abrol®SR 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 working with 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.***
Unless otherwise specified it is recommended to take the drug Abrol®SR as follows:
*Adults and adolescents from 12 years:* 1 tablet once a day (equivalent to 75 mg/day ambroxol hydrochloride) in the morning ***or*** in the evening after meals. Tablets should be swallowed whole, with enough water.
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 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 tablet. 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 on specific symptoms of overdose. Symptoms known from isolated reports on overdose and/or cases of using preparation by mistake correspond to the known adverse effects of ambroxol in the recommended doses and require symptomatic treatment.

***Adverse reactions.***
*Immune system disorders:* hypersensitivity reactions, anaphylactic reactions including anaphylactic shock, angioedema and pruritus.
*Skin and subcutaneous tissue disorders:* rash, urticaria, Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

*Nervous system disorders:* dysgeusia (changed taste).
*Gastrointestinal disorders:* nausea, decreased sensitivity in the mouth, vomiting, diarrhea, dyspepsia, abdominal pain, dry mouth, dry throat, salivation.
*Respiratory, thoracic and mediastinal disorders:* pharyngeal hypaesthesia, dyspnoea (as a hypersensitivity reaction).
*General disorders:* fever, reactions in mucous membranes.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

***Shelf life.***
3 years.

**Storage conditions.**
Store at the temperature not more than 25 °C in the original package.
Keep out of reach of children.

**Package.**
10 tablets are in a blister; 1 or 2 blisters are in a carton pack.

**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.**
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