

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product: AMBER

2. Qualitative and Quantitative Composition

Composition of the Drug product:

Each film coated tablet contains:

Ambroxol Hydrochloride..... 30 mg

Lactose Monohydrate

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablets for oral use.

White colored, round shaped, biconvex, film coated tablets.

4. Clinical particulars

4.1. Therapeutic indications

Secretolytic therapy in acute and chronic bronchopulmonary diseases associated with impaired mucus formation and transport.

4.2. Posology and method of administration

Unless otherwise prescribed, the following doses are recommended for AMBER tablets 30 mg:

Children from 6 to 12 years of age:

The usual dose is ½ a tablet 2 - 3 times daily (equivalent to 2 - 3 x 15 mg ambroxol hydrochloride per day).

Adults and adolescents over 12 years of age:

The usual dose is 1 tablet 3 times daily (equivalent to 3 x 30 mg ambroxol hydrochloride per day) for the first 2 - 3 days and 1 tablet twice daily (equivalent to 2 x 30 mg ambroxol hydrochloride per day) thereafter.

For adults and adolescents over 12 years of age, the therapeutic effect may be enhanced by increasing the dose to 2 tablets twice daily (equivalent to 120 mg ambroxol hydrochloride per day).

AMBER tablets 30 mg can be taken with or without food and should be swallowed whole with sufficient amounts of liquid (e.g., Water, tea or fruit juice).

There is no restriction in principle on the duration of use, although longer-term administration requires medical supervision. The package leaflet informs patients that AMBER tablets 30 mg should not be taken for more than 4 - 5 days without medical advice.

4.3. Contraindications

AMBER tablets 30 mg are contraindicated in patients with known hypersensitivity to ambroxol hydrochloride or to any of the excipients.

AMBER tablets 30 mg are not suitable for children under 6 years of age on account of their strength.

Ambroxol pediatric syrup 15 mg/5ml is available for use in children under 6 years of age.

4.4. Special warnings and precautions for use

Severe skin reactions have been reported, such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis in patients taking ambroxol. You need to stop using immediately medicine if symptoms of a progressive skin rash appear (sometimes with blistering or lesions of the mucous membranes of the mouth, pharynx, nose, eyes, genitals) and seek immediate medical attention. In addition, during the early phase of Stevens-Johnson syndrome or TEN, patients may initially experience non-specific influenza-like symptoms such as fever, joint pain, rhinitis, cough and sore throat. Because of these non-specific influenza-like initial symptoms, symptomatic treatment with cough and cold medications, which is inappropriate, may be started.

In patients with impaired bronchial motility and copious secretions (as seen, for instance, in the rare syndrome of primary ciliary dyskinesia), AMBER tablets 30 mg should be used with caution because of the risk that they may promote accumulation of secretions.

Ambroxol must not be used in patients with impaired renal function or severe liver disease except on medical advice. With Ambroxol, as with any active substance which is metabolized in the liver and then eliminated via the kidneys, accumulation of the metabolites which are formed in the liver can be expected to occur in patients with severe renal impairment.

Each tablet contains lactose Monohydrate. Patients with the rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should therefore not take AMBER tablets 30 mg.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant administration of AMBER tablets 30 mg and cough suppressants may lead to the development of a dangerous accumulation of secretions owing to attenuation of the cough reflex and should be undertaken only after careful risk-benefit assessment.

4.6. Fertility, pregnancy and lactation

Pregnancy

Ambroxol hydrochloride crosses the placental barrier. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Extensive clinical experience after the 28th week of pregnancy has shown no evidence of harmful effects on the fetus. However, the usual precautions concerning the

administration of any drug during pregnancy should be observed. The use of Ambroxol is not recommended during the first trimester of pregnancy in particular.

Lactation

Ambroxol has been shown to be excreted in the milk in animal studies. Use during lactation is not recommended.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7. Effects on ability to drive and use machines

There is no evidence of any effect on the ability to drive or use machines. No relevant studies have been performed.

4.8. Undesirable effects

The following categories are normally used when reporting the frequencies of side effects:

Very common	More than 1 in 10 patients
Common	Between 1 in 10 and 1 in 100 patients
Uncommon	Between 1 in 100 and 1 in 1000 patients
Rare	Between 1 in 1000 and 1 in 10.000 patients
Very Rare	Fewer than 1 in 10.000 patients
Not known	Frequency cannot be estimated from the available data

Side effects

Immune system disorders

Rare: hypersensitivity reactions

Not known: anaphylactic reactions, including anaphylactic shock, angioedema (rapidly developing swelling of the skin, subcutaneous tissue, mucous membrane or submucosa), itching.

Nervous system disorders

Common: Taste disturbances

Gastrointestinal disorders

Common: Nausea, feeling of numbness in the mouth,

Uncommon: Vomiting, diarrhea, indigestion, abdominal pain, dry mouth, dyspepsia

Rare: Dry throat.

Very rare: Constipation, increased salivation

Respiratory thoracic and mediastinal disorders

Common: Feeling of numbness in the throat

Very rare: Increased nasal discharge

Not known: Shortness of breath (as symptom of a hypersensitivity reaction).

Skin and subcutaneous tissue disorders

Rare: rash, urticaria.

Not known: severe skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis).

Renal and urinary disorders

Very rare: Difficulty urinating

General disorders and administration site conditions

Uncommon: Fever, mucous membrane reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Health care professionals are required to report any suspected adverse reactions online to the Center of Drug and Medical Technologies Expertise of MOH of RA via pharm.am or call the hotline numbers: (+374 10) 20-05-05, (+374 96) 22-05-05.

4.9 Overdose

No specific symptoms of overdose have been reported to date. The symptoms observed in cases of accidental overdose or medication error are consistent with the undesirable effects which may occur at recommended doses and may require symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics

ATC code: R05CB06

It has been shown in preclinical studies that Ambroxol hydrochloride, the active substance increases the serous component of bronchial secretions. It also increases surfactant production by virtue of a direct effect on type II pneumocytes in the alveoli and Clara cells in the small airways, as well as stimulating the activity of the ciliated epithelium. These actions result in decreased mucus viscosity and improved mucociliary clearance. The improvement in mucociliary clearance has been demonstrated in clinical pharmacology studies.

Increased production of serous secretions and enhanced mucociliary clearance facilitate expectoration and ease cough.

In patients with COPD who were given Ambroxol prolonged-release capsules 75 mg for 6 months, there was a significant reduction in exacerbations, compared to placebo, by the end of the 2nd month of treatment. Patients in the Ambroxol group lost significantly fewer days through illness and had fewer days when they needed antibiotic therapy. They also experienced a statistically significant improvement in symptoms, measured as difficulty in expectoration, cough, dyspnoea and auscultatory signs, compared to placebo.

A local anesthetic effect of ambroxol hydrochloride has been observed in the rabbit eye model and is probably due to the drug's sodium channel blocking properties. In-vitro tests showed that the drug blocks cloned voltage-dependent neuronal sodium channels; binding was reversible and concentration dependent.

Ambroxol hydrochloride has been found to have an anti-inflammatory effect in vitro. In in-vitro tests, it significantly reduced cytokine release from circulating and tissue-bound mononuclear and polymorphonuclear cells.

Clinical studies in patients with sore throat showed that ambroxol hydrochloride significantly reduces pharyngeal pain and redness.

These pharmacological properties are consistent with the ancillary observation from clinical efficacy studies that inhaled ambroxol provides rapid relief of pain when used in the treatment of upper respiratory tract disorders.

Administration of ambroxol hydrochloride increases the concentrations of the antibiotic's amoxicillin, cefuroxime, erythromycin and doxycycline in sputum and bronchial secretions. To date, this has not been shown to have any clinical relevance.

5.2 Pharmacokinetic properties

Absorption:

Absorption of ambroxol hydrochloride from rapid-release oral dosage forms is rapid and complete and is dose-linear in the therapeutic range. Peak plasma levels are reached within 1 - 2.5 h following administration of immediate-release dosage forms and after a median of 6.5 h following administration of slow-release dosage forms.

Absolute bioavailability following administration of a 30-mg tablet is 79%. The dose-normalized relative bioavailability of the prolonged-release capsule is 95% when compared to the non-modified release tablet form (60 mg daily, given as 2 x 30 mg doses).

Distribution:

Distribution of ambroxol hydrochloride from the blood to the tissues is rapid and pronounced, with the highest concentrations being found in the lungs. The estimated distribution volume following oral administration is 552 l.

Plasma protein binding in the therapeutic range is approximately 90%.

Metabolism and elimination:

Approximately 30% of an orally administered dose is eliminated by first-pass metabolism.

Ambroxol hydrochloride is metabolized primarily in the liver by glucuronide conjugation and cleavage to dibromoanthranilic acid (the latter accounting for about 10% of the dose). Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol hydrochloride to dibromoanthranilic acid.

Three days after oral administration, about 6% of the dose is eliminated in unchanged form and about 26% in conjugated form in the urine.

The terminal elimination half-life of ambroxol hydrochloride is about 10 h. Total clearance is approximately 660 ml/min, with renal clearance accounting for about 83% of this figure.

Pharmacokinetics in special populations:

In patients with impaired hepatic function, elimination of ambroxol hydrochloride is reduced, resulting in an approximately 1.3- to 2-fold increase in plasma levels. In view of the high therapeutic index of the drug, adjustment of the dose is not necessary.

The pharmacokinetics of ambroxol hydrochloride are not modified to any clinically significant extent by either age or gender. No adjustments to the recommended dosage are therefore required. The bioavailability of ambroxol hydrochloride is not affected by food consumption.

5.3 Preclinical safety data

Ambroxol has a low acute toxicity index.

Oral use: Repeated-dose toxicity studies in rats (52 and 78 weeks), rabbits (26 weeks), mice (4 weeks) and dogs (52 weeks) did not identify any target organ toxicity. The no observed adverse effect level (NOAEL) was 50 mg/kg/day in rats, 40 mg/kg/day in rabbits, 150 mg/kg/day in mice and 10 mg/kg/day in dogs.

Intravenous use: Four-week toxicity studies which included a histopathological assessment were carried out in rats using doses of 4, 14 and 64 mg/kg/day (infused for 3 h/day) and in dogs using doses of 45, 90 and 120 mg/kg/day (infused for 3 h/day). These studies revealed no serious local or systemic toxicity; all adverse effects were reversible.

Ambroxol hydrochloride was neither embryotoxic nor teratogenic when tested at oral doses of up to 3000 mg/kg/day in rats and up to 200 mg/kg/day in rabbits. The fertility of male and female rats was not impaired following doses of up to 1500 mg/kg/day.

The NOAEL in a study on peri- and postnatal development was 50 mg/kg/day.

A dose of 500 mg/kg/day was slightly toxic for both dams and young animals, causing delayed weight gain and reduced litter size.

In genotoxicity studies, no evidence of any mutagenic potential was found either in vitro (Ames test and chromosome aberration test) or in vivo (micronucleus test in mice).

In carcinogenicity studies, no evidence of any tumorigenic potential was seen when ambroxol hydrochloride was given as a dietary admixture to mice at doses of 50, 200 and 800 mg/kg/day over 105 weeks and to rats at doses of 65, 250 and 1000 mg/kg/day over 116 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize Starch, Lactose Monohydrate, Povidone K-30 %, Purified Water, Purified Talc, Magnesium stearate, Colloidal silicon Dioxide, Sodium Starch Glycollate, Isopropyl alcohol, Titanium Dioxide (E171), Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store in a dry place below 25°C.

Keep all medicines out of reach of children.

6.5. Nature and contents of container

10 Film-coated tablets are packed in Alu/PVC blister, such 2 or 10 blisters are packed in carton along with insert.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with national requirements.

7. MANUFACTURER AND MARKETING AUTHORISATION HOLDER

A LAB PHARMACEUTICALS, LLC

Nor Nork, Kochinyan 13/16, Yerevan, Republic of Armenia

Phone: +374-11-981000

Email: info@alab.am

Postal code: 0089

8. MARKETING AUTHORISATION NUMBER

Not available

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Not Available

10. DATE OF REVISION OF THE TEXT

19.03.26

11. GENERAL CLASSIFICATION FOR SUPPLY

Without prescription Medicine