

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Abrobion_15 mg/5 ml & 30 mg/5 ml Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

trans-4-[(2-amino-3,5-dibromobenzyl) amino] cyclohexanol hydrochloride
(=Ambroxol hydrochloride)

Syrup 15 mg/5 ml

5 ml of syrup contain 15 mg Ambroxol hydrochloride.

Syrup 30 mg/5 ml

5 ml of syrup contain 30 mg Ambroxol hydrochloride.

Excipients with known action
Sorbitol (E-420), Menthol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

As an aid in the liquidification of mucous secretion of the respiratory tract in cases of acute and chronic bronchopulmonary conditions (bronchitis, emphysema, tracheobronchitis, chronic asthmatic bronchitis).

It is also indicated for the prevention of respiratory complications after retention of secretion after major surgical operations in the thorax-upper abdomen and after long term bed-rest.

During acute exacerbations of bronchitis, it should be administered along with the appropriate antibiotic.

4.2. Posology and method of administration

Dosage

Syrup 15 mg/ 5ml:

Adults and children above 12 years: 30 mg (2 teaspoons or 10 ml with the dosimetric spoon included in the package). 3 times daily

Children 6-12 years: 15 mg (1 teaspoon or 5 ml with the dosimetric spoon included in the package). 2-3 times daily

Children 2-5 years: 7.5 mg (1/2 teaspoon or 2.5 ml with the dosimetric spoon included in the package). 3 times daily.

1 teaspoon is equivalent to 5ml with the dosimetric spoon included in the package.

Syrup 30 mg/ 5ml:

Adults and children above 12 years: 30-60 mg (1-2 teaspoons or 5-10 ml with the dosimetric spoon included in the package). 2-3 times daily

Children 6-12 years: 15 mg (1/2 teaspoon or 2,5 ml with the dosimetric spoon included in the package). 2-3 times daily

Children 2-5 years: 7.5 mg (1/4 teaspoon or 1.25 ml with the dosimetric spoon included in the package). 3 times daily.

1 teaspoon is equivalent to 5ml with the dosimetric spoon included in the package.

Duration of therapy

The advice of the treating doctor must be sought if the symptoms do not subside after 4-5 days or worsen during treatment.

Method of administration

Oral administration

It should be taken with an adequate amount of liquid (preferably a glass of water)

The effectiveness of this medicine is independent from the food intake. However, it is recommended to be received after meals to prevent the appearance of undesirable effects in the gastrointestinal system.

The patients should be informed for an expected increase in the flow of secretions. The consumption of an adequate amount of fluids is recommended during the day.

Paediatric population

In children between 2 and 6 years old it should be administered under medical supervision. Use is contraindicated in children below 2 years old.

Additional information for special populations

Abrobion due to its composition (it does not contain sugar) is appropriate for use in diabetics.

4.3. Contraindications

Hypersensitivity to the active substance (ambroxol hydrochloride) or to any of the excipients listed in section 6.1

It should not be administered during pregnancy and lactation.

It is contraindicated in rare hereditary conditions, in which the patient may show intolerance to some of the product's excipients (see paragraph 4.4).

The use of ambroxol hydrochloride in children below 2 years old is contraindicated.

Mucolytics can cause bronchial obstruction to children of age less than 2 years old. In reality, the ability to remove the bronchial mucus is limited in this age group, due to the physical characteristics of the respiratory route. Therefore, it should not be used in children less than 2 years old.

4.4. Special warnings and precautions for use

It should be administered with caution to patients with active or history of gastric duodenal ulcer and to asthmatic patients with a history of bronchospasms or severe respiratory insufficiency or active tuberculosis.

During use of this medicine increase on the volume of thinning bronchial secretion can be induced and if this cannot be removed by coughing it is preferable for the patient to be intubated so that the respiratory tract remains open.

There have been reports of severe skin reactions 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 symptoms or 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.

Most cases can be explained by the severity of other underlying diseases and/or concomitant medical treatment. In addition, during the early phase of a Stevens-Johnson Syndrome or toxic epidermal necrolysis a patient can first experience non-specific influenza-like prodromes like e.g. fever, aching body, rhinitis, cough and sore throat. These non-specific influenza-like prodromes are possible to mislead to the beginning of a symptomatic treatment for cough and cold.

In case of impaired renal function or severe hepatic impairment Abrobion can be used only after medical advice. Like all medicines metabolized by the liver which follow renal excretion, accumulation of ambroxol metabolites formed in the liver may occur, when severe renal failure exists.

Abrobion Syrup 30 mg/5ml: 5ml of syrup contain 1.6g sorbitol (E-420) which results in 6.4g sorbitol per maximum daily dose (20 ml). Patients with rare hereditary problems of fructose intolerance should not take this medicine. May also have a mild laxative effect.

Abrobion Syrup 15 mg/5ml: 5ml of syrup contain 1.6g sorbitol (E-420) which results in 9.6g sorbitol per maximum daily dose (30 ml). Patients with rare hereditary problems of fructose intolerance should not take this medicine. May also have a mild laxative effect.

Abrobion Syrup 30 mg/5ml & 15 mg/5ml contain menthol. Menthol can cause apnoic reflex and/or laryngospasm (Kratchmer reflex) in children below 2 years old, then it comes in contact with nasal mucosa (especially if the syrup comes into contact with the nostrils or near the nose). Therefore, its use in this age group is not recommended. Despite that in case that such symptoms appear doctors advise should be immediately sought due to their potential seriousness.

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

There are no clinically relevant unfavourable interactions with other medicines.

After ambroxol administration antibiotics' concentrations (amoxicilline, cefuroxime, erythromycin) in bronchopulmonary excretions and saliva are increased.

Concomitant administration of an anti-cough medicine suppresses the cough reflex and can cause stasis of the thinning- due to the ambroxol- mucous.

4.6. Fertility, pregnancy and lactation

Pregnancy

Ambroxol hydrochloride crosses the placenta.

Non-clinical trials have not shown direct or indirect harmful effect regarding gestation, embryonic development, labor or the post-natal development. Extensive clinical experience after the 28th week of pregnancy has not shown any harmful

effects to the fetus. However, usual precautions relative to the use of medicines during pregnancy have to be taken.

Use of Abrobion **is not recommended** during pregnancy, especially during the first trimester of pregnancy.

Breastfeeding

Ambroxol hydrochloride is excreted in breast milk.

Although no undesirable effects to nursing infants are expected, ambroxol hydrochloride administration to nursing mothers **is not recommended**.

Fertility

Non-clinical studies do not show direct or indirect harmful effects related to fertility.

4.7. Effect on ability to drive and use machines

There are no indications on post-marketing data for influence on the ability to drive and use machines. No studies have been conducted relative to the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are arranged according to the frequency of appearance as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1.000$ to $< 1/100$)

Rare ($\geq 1/10.000$ to $< 1/1.000$)

Very rare ($< 1/10.000$)

Not known (cannot be estimated from the available data)

Immune system disorders

Rare: hypersensitivity reactions

Not known: anaphylactic reactions including anaphylactic shock, angioedema and pruritus

Skin and subcutaneous tissue disorders

Rare: rash, urticaria

Not known: Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

Nervous system disorders

Common: Dysgeusia (e.g. altered taste)

Gastrointestinal disorders

Common: Nausea, mouth hypesthesia

Not common: vomiting, diarrhea, dyspepsia, abdominal pain, xerostomia

Rare: Stomach burning, pharyngeal dryness.

Respiratory, thoracic and mediastinal disorders

Common: pharyngeal hypesthesia

Not known: bronchospasm (as a symptom of hypersensitivity reaction)

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 online to the **Center of Drug and Medical Technologies Expertise** of MoH of RA via www.pharm.am or call the hotline numbers: +374 10 20 05 05 and +374 96 22 05 05.

4.9. Overdose

Symptoms

No specific overdose symptoms with ambroxol have been reported so far in humans.

Treatment

Based on observations in accidental overdose and medication error reports, observed symptoms are in accordance with the known undesirable effects of ambroxol hydrochloride in the recommended dosage and symptomatic treatment may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Expectorants excluding combinations with cough suppressants, Mucolytic.

ATC code: R05CB06

Preclinically, ambroxol hydrochloride, the active ingredient of Abrobion has been shown to increase the secretion of the respiratory tract. Enhances the production of the surface-acting agent in the lungs and the function of cilia. These actions have as a result the improvement of the flow and transport of mucus (mucociliary clearance). Improvement of mucociliary clearance has been proven in clinical pharmacology studies. The increase in secretions and mucociliary clearance facilitate expectoration and relieve from cough.

In patients suffering from COPD (Chronic Obstructive Pulmonary Disease), long-term treatment (6 months) with ambroxol hydrochloride (prolonged release capsules 75 mg) led to significant reduction of exacerbations which became apparent after 2-month treatment. Patients in the treatment group with ambroxol hydrochloride lost significantly less day's due to illness and had less days on antibiotic treatment, when needed. Treatment with ambroxol hydrochloride prolonged release capsules also caused a statistically significant improvement of symptoms (difficulty in expectoration, cough, dyspnea, auscultatory signs) in comparison with placebo.

Topical anesthetic action of ambroxol hydrochloride has been observed in rabbit eye model, which can be explained by properties it has on the sodium channel block. Ambroxol hydrochloride has been proved to block sodium channels *in vitro*; this block is reversible and dependent on the concentration of the substance.

Cytokines release in blood as well as the mononuclear and polymorphonuclear cells attached to tissues seem to be reduced significantly *in vitro* by ambroxol hydrochloride.

In clinical studies in patients with sore throat, pain in the pharynx and redness were significantly reduced after ambroxol lozenge administration.

After ambroxol administration antibiotic concentrations (amoxicillin, cefuroxime, erythromycin) in brochopulmonary secretions and saliva are increased.

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies have shown rapid absorption of orally administered immediate release forms of ambroxol hydrochloride, with linearity in the therapeutic dose range. Maximum plasma concentrations are reached within 1 to 2.5 hours for the oral immediate release forms and 6.5 hours for the slow release forms.

Absolute bioavailability after administration of a 30 mg tablet was found to be 79%. Slow release capsule shows relative bioavailability of 95% (normalized dose) in comparison to the immediate release tablet of 30 mg (daily dose 60mg, 30 mg twice daily).

Distribution

Protein binding at plasma therapeutic levels is approximately 90%. Distribution of ambroxol from blood to tissues after oral, i.v. and i.m. administration is rapid and the maximum concentrations of the medicine are observed in the lungs. Volume of distribution after oral administration was estimated to be 552 L.

Biotransformation and Elimination

Approximately 30% of the orally administered dose is eliminated via the first pass effect.

Studies in human hepatic microsomes have shown that CYP3A4 coenzyme is responsible for the metabolism of ambroxol hydrochloride to dibromoanthranilic acid. This metabolite and the mother compound (ambroxol) are transformed in conjugation products mainly glucuronides. Within 3 days after oral administration, approximately 6 % of the dose is found in free form, while approximately 26% of the dose is found in the conjugated form in urine.

Plasma half-life approximates 10 hours. Total clearance is around 660 mL/min, with renal clearance to account for about 83% of the total clearance.

Pharmacokinetics in special population

In patients with impaired hepatic function, elimination of ambroxol hydrochloride is reduced, resulting to plasma levels 1.3 to 2 times higher. Due to the wide therapeutic range of ambroxol hydrochloride, dosage adjustment is not required.

Age and sex does not seem to affect ambroxol hydrochloride pharmacokinetics in the clinical level and therefore dose adjustment is not required.

Food was not found to affect the bioavailability of ambroxol hydrochloride.

5.3 Preclinical safety data

Ambroxol has a low acute toxicity index.

Repeated-dose studies with a dose of 150 mg/kg/day in mice (4 weeks), with a dose of 50 mg/kg/day in rats (52 and 78 weeks), with a dose of 40 mg/kg/day in rabbits (26

weeks) and with a dose of 10 mg/kg/day in dogs (52 weeks) was representative of the No Observed Adverse Effect Level (NOAEL).

Intravenous use 4 weeks toxicity studies with ambroxol hydrochloride where 4, 16 και 64 mg/kg was administered to rats and 45, 90 και 120 mg/kg was administered to dogs (infusions of 3 hours/day) have not shown any serious topical or systematic toxicity including histopathological lesions. All undesirable effects were reversible.

Administration of high doses of oral ambroxol hydrochloride up to 3000 mg/kg/day in rats and 200 mg/kg/day in rabbits hasn't shown embryotoxic or teratogenic action. Fertility of male and female rats was not affected with doses up to 500 mg/kg/day.

NOAEL in a peri- and post-natal development study was 50 mg/kg/day. Ambroxol hydrochloride dose of 500 mg/kg/day was slightly toxic to dogs, since they showed decreased body weight.

Genotoxicity studies *in vitro* (Ames test and Chromosome aberration test) as well as *in vivo* (mice micronucleus test) did not show any mutagenic potential of ambroxol hydrochloride.

Ambroxol hydrochloride did not show any tumorigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg/day) and rats (65, 250 and 1000 mg/kg/day), the duration of which was 105 and 116 weeks respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Syrup 15 mg/5ml & Σιρόπι 30 mg/5ml

Hydroxyethylcellulose, Sorbitol solution 70% (E-420), Glycerol solution 85%, Benzoic acid, Propylene glycol, Saccharin sodium, Menthol, Cherry flavor, Water purified.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Abrobion Syrup 15mg/5ml is available in an amber glass bottle of 125ml volume with plastic safety cap and dosimetric spoon.

Abrobion Syrup 30mg/5ml is available in an amber glass bottle of 125ml or 200ml volume with plastic safety cap and dosimetric spoon.

Not all strengths and/or packages may be marketed

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

HELP S.A., 10 Valaoritou, 144 52 Metamorphosis Attica, Tel.: +30 210 281 5353

8. MARKETING AUTHORISATION NUMBER:

Syrup 15 mg/ 5ml: 42066/09/12-02-2010, 20115/16/24-2-2017

Syrup 30 mg/ 5ml: 84722/30-09-2014, 20115/16/24-2-2017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 1999

Date of latest renewal: 12 February 2010

10. DATE OF REVISION OF THE TEXT

24-02-2017