

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ambrobene Extra Strength 6 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains:
6 mg of ambroxol hydrochloride.

Excipient(s) with known effect:

Sorbitol liquid (E420): 245 mg of sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear, colourless oral solution with raspberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

A mucolytic therapy for the treatment of airway diseases associated with abnormal mucous secretion and transport disturbances affecting mucous secretion and clearance in adults and children older than 2 years of age.

4.2 Posology and method of administration

Posology

The following dosages are recommended for Ambrobene Extra Strength 6 mg/ml Oral Solution (5 ml dose = one syringe):

Paediatric population:

Children under 2 years: Ambrobene is contraindicated.

Children from 2 to 5 years: Take 1.25 ml (a quarter of a syringe) of Ambrobene 6 mg/ml 3-times a day (every 8 hours) (equivalent to 22.5 mg of ambroxol hydrochloride per day).

Children from 6 to 12 years: Take 2.5 ml (half a syringe) of Ambrobene 6 mg/ml 2 to 3 times a day (every 12 or 8 hours) (equivalent to 30-45 mg of ambroxol hydrochloride per day).

Adults and children over 12 years:

Typically, during the first 2 to 3 days 5 ml (one syringe) of Ambrobene 6 mg/ml should be taken 3 times daily (every 8 hours) (corresponding to 90 mg of ambroxol hydrochloride per day). After that, take 5 ml (one syringe) of Ambrobene 6 mg/ml twice a day (every 12 hours) (equivalent to 60 mg ambroxol hydrochloride per day).

At the dosage for adults and children over 12 years, an increased effectiveness is possible with the dosage of 10 ml 6 mg/ml Ambrobene two times a day (every 12 hours) (corresponding to 120 mg of ambroxol hydrochloride per day).

Renal impairment: see section 4.4.

Hepatic impairment: see section 4.4.

Method of administration

Oral use only.

Ambrobene should be taken after meals, with the help of the attached dosing device (oral syringe).

It is recommended to drink a glass of water after administration and plenty of liquid during the day.

If symptoms don't improve or worsen, in 5 days of treatment, medical advice should be sought.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Children up to 2 years
- Patients with rare hereditary problems of fructose intolerance. In case of rare hereditary conditions that may be incompatible with one of the medicinal product's excipients (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

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. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, ambroxol treatment should be discontinued immediately and medical advice should be sought.

In patients with compromised airways motility (e.g. rare cases of primary ciliary dyskinesia) ambroxol oral solution should be cautiously administered due to the risk of potential obstruction of the airways with mucus.

Renal and hepatic impairment

In patients with renal or serious hepatic impairment ambroxol oral solution should be administered with caution (e.g. in lower doses or in longer time intervals).

In patients with serious renal impairment accumulation of hepatic metabolites of ambroxol should be expected.

Caution is required in patients with history of peptic or duodenal ulcers.

In patients with asthma and serious asthmatic attacks, ambroxol oral solution should be used cautiously.

Warning relating to excipients:

Ambrobene also contains 245 mg of sorbitol (E-420) per ml. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combination of ambroxol oral solution with cough suppressants can, due to suppressed cough reflex, cause serious obstruction of the airways.

Administration of ambroxol with antibiotics (amoxicillin, cefuroxim, and erythromycin) leads to increase of antibiotics concentrations in mucus.

No clinically relevant unfavourable interactions with other medications have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of ambroxol in pregnant women, especially in the first 28 weeks of pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Clinical experience to date has shown no evidence of harmful effects on the foetus during pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed. Especially during the first trimester, the use of ambroxol is not recommended.

Breastfeeding

In animal studies, ambroxol is excreted in breast milk. As there are no adequate data from the use of ambroxol in breastfeeding women, ambroxol should be prescribed to breastfeeding women only after careful evaluation of risk and benefit.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with ambroxol hydrochloride.

On the basis of pharmacokinetic profile and reported adverse reactions the medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

- a. Summary of the safety profile
The most frequently adverse reaction is diarrhoea.
- b. Tabulated list of adverse reactions

| System organ class | Adverse event | Frequency |
|---|---|--|
| Immune system disorders | Hypersensitivity reactions | Rare (≥1/10,000 to <1/1000) |
| | Anaphylactic reactions including anaphylactic shock, angioedema and pruritus | Not known (cannot be estimated form the available data) |
| Nervous system disorders | Dysgeusia | Common (≥1/100 to <1/10) |
| Respiratory, thoracic and mediastinal disorders | Pharyngeal hypoesthesia | Common (≥1/100 to <1/10) |
| | Rhinorhea, Dryness of the airways | Very rare (<1/10,000) |
| Gastrointestinal disorders | Diarrhoea, Oral hypoesthesia, Nausea | Common (≥1/100 to <1/10) |
| | Vomiting, Abdominal pain, Dyspepsia, Dry mouth | Uncommon (≥1/1000 to <1/100) |
| | Heartburn, Dry throat | Rare (≥1/10,000 to <1/1000) |
| | Constipation, Sialorrhea | Very rare (<1/10,000) |
| Skin and subcutaneous tissue disorders | Rash, urticaria | Rare (≥1/10,000 to <1/1000) |
| | Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis), | Not known (cannot be estimated from the available data) |

| | | |
|-----------------------------|---------|------------------------------|
| Renal and urinary disorders | Dysuria | Very rare (<1/10,000) |
| General disorders | Fever | Uncommon (≥1/1000 to <1/100) |

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Serious symptoms during overdosage with ambroxol were not recorded. Short-term restlessness and diarrhoea were most common.
Ambroxol administered parenterally up to dose of 15 mg/kg/day and orally up to 25 mg/kg/day was well tolerated. According to the pre-clinical data in the case of extreme overdosage symptoms of sialorrhea, nausea, vomiting and hypotension can be expected.

Treatment

Acute measures, such as administration of an antiemetic and gastric lavage are not generally indicated as those symptoms are to be expected only in extreme cases of overdosing. Treatment of ambroxol overdose should be mainly symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics, ATC code: R05CB06

Ambroxol, a metabolite of bromhexin, is a mucoactive drug with several properties including secretolytic and secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract which play an important role in the body’s defence mechanisms and resulting in more productive cough. The pharmacological effect is exerted on mucus quality, ciliary function and the production of alveolar surfactant.
Mucus quality: ambroxol stimulates the activity of serous glandular cells, clears granules of mucus that have already formed, normalizes secretion viscosity and finally regularizes the activity of the tubuloacinar glands in the respiratory tract.
Ciliary function: ambroxol increases both the number of microvilli in the vibratile epithelium and the frequency of ciliary movements, with a resulting increase in the speed of transport of secretion produced, and finally normalizes respiratory tone, improving expectoration.
Increase in surfactant production: ambroxol stimulates synthesis and release of surfactant by type II pneumocytes in alveolae and in small airways in foetal, as well as in adult lungs, thus ensuring the stability of the lung tissue, allowing correct bronchiolar and alveolar clearance and finally facilitating respiratory mechanics and encouraging gaseous exchanges. Those effects were observed in vitro as well in vivo in different animal species.
In several pre-clinical experiments antioxidative effects of ambroxol were noted. Up to date no clinical relevance of this observation was confirmed.
After ambroxol administration concentrations of antibiotics amoxicilline, cefuroxime, erythromycine and doxycycline were higher in sputum and bronchial secretion, however, without clinical significance.

5.2 Pharmacokinetic properties

The bioavailability of ambroxol has been evaluated in humans after the oral administration of the drug in healthy volunteers.

Ambroxol is almost completely absorbed after oral administration. T_{\max} is 1-3 hours.

It is extensively bound to plasma proteins (90%). Half-time of ambroxol in plasma is 7-12 hours. Sum of half-life of ambroxol and its metabolites in plasma is about 22 hours.

Ambroxol crosses in the amniotic fluid and placenta, and is secreted in breast milk.

Ambroxol is metabolized in the liver. Bioavailability of absorbed ambroxol is lowered by a third due to the first pass metabolism in the liver.

About 90% of ambroxol and its metabolites are eliminated through the kidneys. Less than 10% of ambroxol is eliminated unchanged by the kidneys.

Due to high protein binding and big distribution volume, as well as slow re-release from the tissues in blood dialysis or forced diuresis will be ineffective in elimination of ambroxol.

In patients with severe hepatic impairment clearance of ambroxol lowers 20 – 40%.

In patients with severe renal impairment accumulation of ambroxol metabolites is to be expected.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acesulfame potassium (E950)
Benzoic acid (E210)
Glycerol (E422)
Hydroxyethylcellulose (E1525)
Propylene glycol (E1520)
Sorbitol liquid (E420)
Raspberry flavour
Vanilla flavour
Water purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening of the bottle: 6 months.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the upright position.

6.5 Nature and contents of container

Brown PET bottles with child-resistant PP closure with dosing crimp insert and oral syringe (5 ml syringe graduated every 0.25 ml).

Pack size: 100 ml.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/158/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd May 2013

Date of last renewal: 23rd May 2015

10 DATE OF REVISION OF THE TEXT

August 2016