SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ambroxol <TRADE NAME> <STRENGTH> Syrup

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains <STRENGTH> of ambroxol hydrochloride

For the full list of excipients, see section 6.1.

<REGARDING THE APPROVAL>

1. PHARMACEUTICAL FORM

Syrup <REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   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.

* 1. Posology and method of administration

**Posology**

**Adults and children over 12 years**

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

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

**Paediatric population**

Children 2 – 5 years: The usual dose is 22.5 mg. divided to 3 times a day.

Children 6 – 12 years: The usual dose is 30-45 mg. divided 2 to 3 times a day

Ambroxol is contraindicated for use in children less than 2 years of age.

**Method of administration**

For oral administration.

Should be taken after meals.

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.

* 1. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use in children less than 2 years of age.

* 1. 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 syrup should be cautiously administered due to the risk of potential obstruction of the airways with mucus.

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 should be used cautiously.

**Excipient information**

<REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

Combination of ambroxol 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.

* 1. 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.

**Breast-feeding**

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.

* 1. 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.

* 1. Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥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

**Nervous system disorders**

Common: Dysgeusia

**Respiratory, thoracic and mediastinal disorders**

Common: Pharyngeal hypoesthesia

Very rare: Rhinorhea, Dryness of the airways

**Gastrointestinal disorders**

Common: Diarrhoea, Oral hypoesthesia, Nausea

Uncommon: Vomiting, Abdominal pain, Dyspepsia, Dry mouth

Rare: Heartburn, Dry throat

Very rare: Constipation, Sialorrhea

**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)

**Renal and urinary disorders**

Very rare: Dysuria

**General disorders**

Uncommon: Fever

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 Health Product Vigilance Center; HPVC.

* 1. Overdose

**Symptoms**

Serious symptoms during overdosage with ambroxol were not recorded. Short-term restlessness and diarrhoea were most common.

Ambroxol administered parenteraly 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.

1. PHARMACOLOGICAL PROPERTIES
   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 mformed, 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.

* 1. 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. Tmax 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

* 1. 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.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

Not applicable.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>