

PACKAGE INSERT TEMPLATE FOR AMBROXOL

Brand or Product Name

[Product name] Tablet 30mg

[Product name] Elixir 30mg/5ml

[Product name] Sustained release capsule 75mg

[Product name] Lozenges 15mg

Name and Strength of Active Substance(s)

Ambroxol.....mg

Product Description

[Visual description of the appearance of the product (eg. colour, viscosity etc)

Eg. Clear or almost clear, colourless elixir;

Round, white tablets, both faces flat with beveled edges; one face is scored and impressed with the appropriate code on either side of the score; the other face is impressed with the company symbol.;

Orange-yellow, circular lozenge with a characteristic orange odour.

Pharmacodynamics

Ambroxol is an active N-desmethyl metabolite of mucolytic bromhexine. Preclinically, ambroxol has been shown to increase the quantity and decrease the viscosity of respiratory tract secretions. It enhances pulmonary surfactant production (surfactant activator) and stimulates ciliary motility. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and eases cough.

A local anaesthetic effect of ambroxol has been observed in animals (rabbit) which may be explained by the sodium channel blocking properties. It was shown in vitro that ambroxol blocks neuronal sodium channels; binding was reversible and concentration-dependent.

Clinical efficacy studies for the treatment with ambroxol of upper respiratory tract symptoms have shown rapid relief of pain and pain related discomfort in the ear-nose-trachea region upon inhalation.

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Cytokine release from blood but also tissue-bound mononuclear and polymorphonuclear cells was found to be significantly reduced by ambroxol in vitro.

Lozenges containing ambroxol have been shown to exert significant effects on pain relief in acute sore throat. Additionally redness in sore throat was significantly reduced.

Following the administration of ambroxol, antibiotic concentrations (amoxicilline, cefuroxime, erythromycin) in bronchopulmonary secretions and in the sputum are increased.

Pharmacokinetics

Absorption

Absorption of all non-delayed oral forms of ambroxol hydrochloride is rapid and complete, with dose linearity in the therapeutic range.

Maximum plasma levels are reached within 1 to 2.5 hours following oral administration of the immediate –release formulation and after a median of 6.5 hours of the slow release formulation.

The absolute bioavailability after a 30 mg tablet was found to be 70-80%.

The slow release capsule showed a relative availability of 95% (dose-normalized) in comparison to a daily dose of 60 mg (30 mg twice daily) administered as immediate-release tablet.

Distribution

In the therapeutic range plasma protein binding was found to be approximately 90%. The distribution half life is 1.3 hours. Distribution of ambroxol hydrochloride from blood to tissue is rapid and pronounced, with the highest concentration of the active substance found in the lungs.

The volume of distribution following oral administration was estimated to be 552L.

Metabolism

About 30% of an orally administered dose is eliminated via first pass metabolism.

Studies in human liver microsomes have shown that CYP3A4 enzyme is responsible for the metabolism of ambroxol. Ambroxol hydrochloride is metabolized primarily in the liver by

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glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose) aside from some minor metabolites.

Excretion

Ambroxol hydrochloride is eliminated with a terminal elimination half-life of approximately 10 hours. Total clearance is in the range of 660 ml/min, with renal clearance accounting for approximately 8% of the total clearance.

Pharmacokinetics in special populations

In patients with hepatic dysfunction elimination of ambroxol hydrochloride is reduced, resulting in approximately 1.3 to 2-fold higher plasma levels.

Due to the high therapeutic range of ambroxol hydrochloride, dose adjustments are not necessary.

Others

Age and gender were not found to affect the pharmacokinetics of ambroxol hydrochloride to a clinically relevant extent and thus there is no necessity for adjustment of dosage regimens.

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

Indication

Immediate release tablets, liquid, sustained release capsules

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

Lozenges

To help in clearing airway and control of chesty cough caused by excessive viscid mucous.

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Recommended Dosage

Immediate release tablets/liquid

Adults and children over 12 yrs dosage:

30mg 3 times daily.

The therapeutic effect may be enhanced by administering 60mg 2 times daily.

60mg 2 times daily regimen is suitable for the therapy of acute respiratory tract disorders and for the initial treatment of chronic conditions up to 14 days.

Paediatric dosage (Liquid)

Dosage according to weight: 1.5 to 2 milligrams/kilogram/day in 2 divided doses.

Dosage according to age:

Children 6 - 12 years: 30mg 2 - 3 times daily.

Children 2 - 5 years: 15mg 3 times daily.

Children 1 - 2 years: 15mg 2 times daily.

This dosage regimen is for initial treatment; the dosage may be halved after 14 days.

In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen in the course of therapy.

Tablets should be taken with liquid.

May be taken with or without food.

Controlled release capsules 75mg

Adult dosage

1 capsule (75mg) once daily.

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The capsules should not be opened or chewed, but swallowed whole with ample liquid. The “carrier tablets” which are occasionally present in the stools have released the active substance during their passage through the digestive system and are therefore without significance.

In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen in the course of therapy.

May be taken with or without food.

Lozenges 15mg

Adults:

Suck 2 lozenges (30mg), 3 times daily.

Children 6-12 years:

Suck 1 lozenge (15mg), 3 times daily.

Mode of Administration

Oral

Contraindications

Should not be used in patients known to be hypersensitive to ambroxol hydrochloride or other components of the formulation.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to warnings and precautions), the use of the product is contraindicated.

Warnings and Precautions

There have been very few reports of severe skin lesions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) in temporal association with the administration of expectorants

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such as ambroxol hydrochloride. Mostly these could be explained by the severity of the patient's underlying disease and/or concomitant medication.

In addition during the early phase of a Stevens-Johnson Syndrome or TEN a patient may first experience non-specific influenza-like prodromes it is possible that a symptomatic treatment is started with a cough and cold medication.

Therefore if new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with ambroxol discontinued as a precaution.

In the presence of impaired renal function, use only after consulting a physician.

Young children can choke on lozenges.

Interactions with Other Medicaments

Following the administration of ambroxol, antibiotic concentrations (amoxicilline, cefuroxime, erythromycin) in bronchopulmonary secretions and in the sputum are increased. No clinically relevant unfavourable interaction with other medications has been reported.

Statement on Usage during Pregnancy and Lactation

Pregnancy

Ambroxol hydrochloride crosses the placental barrier. 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.

Lactation

Ambroxol hydrochloride is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, ambroxol is not recommended for use in nursing mothers and should be used only if absolutely necessary.

Adverse Effects / Undesirable Effects

Generally well tolerated.

Gastrointestinal/ Respiratory effects:

Pyrosis, dyspepsia, nausea, vomiting, diarrhoea and abdominal pain.

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Liquid/Lozenges: oral and pharyngeal hypoaesthesia, dry mouth and dry throat.

Nervous system effects:

Liquid: Dysgeusia (e.g. changed taste).

Immunologic/Dermatological effects:

Ambroxol-induced contact dermatitis, anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus, and other hypersensitivity reactions.

Overdose and Treatment

No specific overdose symptoms of overdose have been reported in man to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of ambroxol at recommended doses and may need symptomatic treatment.

Storage Conditions

[eg Store below.... °C]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]

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