

Ambroxol hydrochloride

Ambrolex[®] / Ambrolex[®] OD

PRODUCT DESCRIPTION

Ambroxol (as hydrochloride) (Ambrolex[®]) 7.5mg/1mL Oral Drops: Each mL of straw colored, blackcurrant flavored liquid contains 7.5mg Ambroxol (as hydrochloride). Excipients include sucrose granulated, sorbitol 70%, methylparahydroxybenzoate, propylparahydroxybenzoate, sodium benzoate, citric acid monohydrate, propylene glycol, disodium edetate, thiourea, blackcurrant flavor, deionized water.

Ambroxol (as hydrochloride) (Ambrolex[®]) 15mg/5mL Syrup: Each 5mL of pink colored, blackcurrant flavored liquid contains 15mg Ambroxol (as hydrochloride). Excipients include sucrose granulated, sorbitol 70%, methylparahydroxybenzoate, propylparahydroxybenzoate, sodium benzoate, citric acid monohydrate, propylene glycol, disodium edentate, thiourea, menthol, blackcurrant flavour, soluble ponceu 4R, purified water

Ambroxol (as hydrochloride) (Ambrolex[®]) 30mg/5mL Syrup: Each 5mL of pink colored, blackcurrant flavored liquid contains 30mg Ambroxol (as hydrochloride). Excipients include sucrose granulated, sorbitol, 70%, methylparahydroxybenzoate, propylparahydroxybenzoate, sodium benzoate, citric acid monohydrate, propylene glycol, disodium edentate, thiourea, menthol, blackcurrant flavor, soluble ponceu 4R, deionized water

Ambroxol (as hydrochloride) (Ambrolex[®]) 30mg Tablet: Each white, uncoated circular biconvex tablet marked with "GSK" on one side and breakline on the other contains 30mg Ambroxol (as hydrochloride). Excipients include maize starch, dibasic calcium phosphate, anhydrous microcrystalline cellulose, talc, magnesium stearate, colloidal silicon dioxide

Ambroxol (as hydrochloride) (Ambrolex[®] OD) 75mg Sustained Release Capsule: Each sustained release capsule contains 75mg Ambroxol (as hydrochloride). Excipients include sucrose microgranules, maize starch microgranules, methacrylic acid – methyl methacrylate copolymer 1:1 (Eudragit L100), diethyl phthalate, talc

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group

Expectorants, excl. combinations with cough suppressants, mucolytics

Mechanism of Action and Pharmacodynamic effects

Ambroxol is the active metabolite of bromhexine. Ambroxol causes an increase in secretion in the respiratory tract. It promotes surfactant production and stimulates ciliary activity. These effects assist the flow of mucus and its removal (mucociliary clearance). An improvement in mucociliary clearance was demonstrated in clinical pharmacological studies. The increase in secretion and mucociliary clearance facilitate expectoration and reduce the cough.

In vitro studies ambroxol showed a significant reduction in cytokine release, both in the blood and in mononuclear and polynuclear cells. The clinical relevance of these findings is unclear.

Pharmacokinetics

Absorption

Ambroxol formulations which are not sustained release are absorbed swiftly and almost completely after oral administration. Oral bioavailability is approx. 60% owing to the first-pass effect. Plasma concentrations are in a linear relationship to the dose. Peak plasma levels are attained after 0.5 to 3 hours. Ambroxol modified-release capsules, on the other hand, has delayed absorption ($T_{max} 6.5 \pm 2.2$ h) and a relative bioavailability of 95% compared with the tablets.

Distribution

Plasma protein binding is around 90% in the therapeutic range. After oral, intravenous and intramuscular administration ambroxol is distributed swiftly and extensively from the blood into the tissues. The highest active ingredient concentrations are measured in the lung.

Metabolism

Studies in human liver microsomes showed that CYP3A4 is the predominant isoform for ambroxol metabolism. Otherwise ambroxol is metabolised in the liver mainly by conjugation.

Elimination

Around 30% of an oral dose is eliminated via the first-pass effect. The terminal half-life is about 10 hours. Total clearance is in the region of 660 ml/min, and renal clearance is 8% of total clearance.

Special patient populations

Children, Elderly, Gender

Age and gender do not affect the pharmacokinetics of ambroxol to any clinically relevant extent; therefore adjustment of the dose is unnecessary.

Renal impairment

An accumulation of metabolites (predominantly conjugates of the parent substance) cannot be ruled out in severe renal impairment.

Clinical Studies

Not relevant for this product.

Non-clinical information

No mutagenic, carcinogenic, teratogenic or embryotoxic effects were observed in the usual tests for genotoxicity, carcinogenicity and reproductive toxicity.

INDICATIONS

For the treatment of:

- Acute respiratory tract diseases with impaired formation of secretions, particularly in acute exacerbations of chronic bronchitis, asthmatic bronchitis, bronchial asthma and bronchiectasis.

The following additional indications are also present in some local markets:

- treatment of respiratory disorders associated with viscid mucus such as: pneumonia, otitis media, sinusitis, nasopharyngitis.
- secretolytic therapy for relieving cough in acute and chronic disorders of the respiratory tract associated with pathologically thickened mucus and impaired mucus transport.

DOSAGE AND ADMINISTRATION

Ambroxol (as hydrochloride) (Ambrolex® OD) 75mg Sustained Release Capsule

The capsules should be swallowed whole without chewing after a meal with adequate fluid.

Ambroxol (as hydrochloride) (Ambrolex®) 30mg Tablet

The tablets should be taken after a meal with adequate fluid.

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

Ambroxol (as hydrochloride) (Ambrolex®) 30mg/5mL Syrup

The syrup should be taken with food.

Route of Administration

For oral administration

Adults

Ambroxol (as hydrochloride) (Ambrolex® OD) 75mg Sustained Release Capsule

One capsule once daily

Ambroxol (as hydrochloride) (Ambrolex®) 30mg Tablet

one tablet 3 times daily

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

Ambroxol (as hydrochloride) (Ambrolex®) 30mg/5mL Syrup

10 mL of 15 mg/5 ml syrup 3 times daily or

5 mL of 30 mg/5 ml syrup 3 times daily

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

10 mL 2 times daily. In severe cases, the dose may be increased up to 20 mL 2 times per day

Children

The recommended daily dose is 1.2-1.6 mg/kg bodyweight.

Children under 2 years of age only when prescribed by a doctor:

Ambroxol (as hydrochloride) (Ambrolex®) 7.5mg/1mL Oral Drops

5 – 10 drops 3 times daily

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

2.5mL 2 times daily

Children aged 2 to 5 years

Ambroxol (as hydrochloride) (Ambrolex®) 7.5mg/1mL Oral Drops

10 – 20 drops 3 times daily

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

2.5 mL 3 times daily

Children aged 6 to 11 years

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

5mL 3 times daily

Ambroxol (as hydrochloride) (Ambrolex®) 30mg Tablet

½ tablet 3 times daily

The following additional Dosage and Administration information is also present in some local markets:

Double Strength syrup is for initial treatment; the dosage may be halved after 14 days.

• **Initial treatment**

Ambroxol (as hydrochloride) (Ambrolex®) 30mg/5mL Syrup

Children aged 1 to 2 years

2.5mL 2 times daily

Children aged 2 to 6 years

2.5mL 3 times daily

Children aged 6 to 12 years

5mL 2 to 3 times daily

Adults and children over 12 years

5mL 3 times daily

• **Treatment continuation**

Ambroxol (as hydrochloride) (Ambrolex®) 15mg/5mL Syrup

Children aged 1 to 2 years

2.5mL 2 times daily

Children aged 2 to 6 years

2.5mL 3 times daily

Children aged 6 to 12 years

5mL 2 to 3 times daily

Elderly

There are no relevant data available.

Renal impairment

In severe renal impairment ambroxol must only be used under medical supervision.

In severe renal impairment, maintenance therapy should be reduced or the dosing interval extended (see Section Warnings and Precautions). The secretolytic effect of ambroxol is supported by adequate fluid intake.

Hepatic impairment

In severe hepatic impairment ambroxol must only be used under medical supervision.

CONTRAINDICATIONS

Ambroxol is contraindicated in:

- hypersensitivity to ambroxol or any of the excipients.

WARNINGS & PRECAUTIONS

Renal impairment

In severe renal impairment, accumulation of metabolites formed in the liver must be expected and consequently the maintenance dose must be reduced or the dosing interval extended.

Secretion impairment

In patients with symptoms of chronic impairment of secretion production or secretion clearance, ambroxol should be used only when prescribed by a doctor.

Peptic ulcers

The use of ambroxol should be carefully considered in patients predisposed to peptic ulcers.

Ciliary dyskinesia

In patients with ciliary dyskinesia the benefit of liquefaction of secretions should be carefully weighed against the risk of congestion of secretions.

Antitussives

Concomitant administration of antitussives should be avoided due to the risk of congestion of secretions (*see Section Interactions*).

Skin damage (see Section Adverse Reactions)

Very rare cases of severe skin damage such as Stevens-Johnson syndrome and Lyell's syndrome have been reported in a temporal relationship with the administration of mucolytic substances such as ambroxol. In most cases they could be explained by the severity of the underlying disease or concomitant administration of another medicine.

If there is a new occurrence of damage to the skin or mucosa, medical advice should be obtained immediately and the treatment with ambroxol should be discontinued.

Excipients

Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Syrup contains sucrose and sorbitol, oral drops contain sorbitol and modified-release capsules contain sucrose. Patients with fructose intolerance should not take this medicine. A mild laxative effect may also occur.

Syrup contains methyl and propyl hydroxybenzoate (parabens) which may cause allergic reactions (possibly delayed).

Syrup and oral drops contain Ponceu 4R (E 124) which may cause allergic reactions.

Ability to perform tasks that require judgement, motor or cognitive skills

No studies on the effects on the ability to drive and use machines have been performed. An effect on the ability to drive and operate machines is unknown.

DRUG INTERACTIONS

Antitussives

Concomitant administration of antitussives may impair the expectoration of liquefied bronchial mucus due to inhibition of the cough reflex and cause congestion of secretions (*see Section Warnings and Precautions*).

Antibiotics

After using ambroxol the concentrations of the antibiotics amoxicillin, cefuroxime and erythromycin in bronchial secretions and sputum are increased.

PREGNANCY AND LACTATION

Fertility

There are no relevant data available.

Pregnancy

Caution is advised when ambroxol is used during pregnancy. Use during the first trimester of pregnancy is not recommended.

Ambroxol crosses the placenta. Animal studies do not show either a direct or indirect harmful effect on pregnancy, embryofoetal development, parturition or postnatal development. Comprehensive controlled studies in pregnant women after the 28th week have not shown any harmful effects on the foetus.

Lactation

Ambroxol is excreted in breast milk and should not be taken during lactation.

However, no adverse effects on the breastfed infant are expected.

ADVERSE EFFECTS

Clinical Trial Data

Not relevant for this product.

Post Marketing Data

Adverse reactions are ranked under headings of frequency using the following convention:

Very common $\geq 1/10$

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

Uncommon $\geq 1/1000$ to $< 1/100$

Rare $\geq 1/10000$ to $< 1/1000$

Very rare $< 1/10000$

Not known (cannot be estimated from the available data).

Immune system disorders (see also Skin and subcutaneous tissue disorder)

Uncommon: allergic reactions

Not known: anaphylactic reactions (facial swelling, respiratory distress, increase in temperature, shivering, including anaphylactic shock)

Respiratory, thoracic and mediastinal disorders

Rare: rhinorrhoea

Gastrointestinal disorders

Common: diarrhoea

Uncommon: nausea, vomiting, other mild gastrointestinal symptoms

Rare: hypersalivation, heartburn, constipation

Skin and subcutaneous tissue disorders

Very rare: severe skin damage such as Stevens-Johnson syndrome and Lyell's syndrome (see Section Warnings and Precautions).

Not known: skin rashes, urticaria, angioedema

Renal and urinary disorders

Rare: dysuria

OVERDOSAGE AND TREATMENT

Symptoms and signs

Manifestations of poisoning are so far unknown in humans.

Treatment

Symptomatic treatment is recommended.

STORAGE CONDITION

Store at temperatures not exceeding 30°C. Protect from light.

AVAILABILITY

* *Ambrolex*[®] 7.5mg/mL *Infant Drops*: Bottles of 15mL.

* *Ambrolex*[®] 15mg/5mL *Syrup*: Bottles of 60 and 120mL.

* *Ambrolex*[®] 30mg/5mL *Syrup*: Bottles of 60 and 120mL.

* *Ambrolex*[®] 30mg *Tablet*: Cartons of 100 tablets.

** *Ambrolex*[®] OD 75mg *Sustained Release Capsule*: Box of 50's.

CAUTION

Keep all medicines out of reach of children.

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