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, menthol, blackcurrant flavor, soluble ponceu 4R, 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 edetate, thiourea, menthol, blackcurrant flavor, soluble ponceu 4R, deionized 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 edetate, 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 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 (Tmax 6.5 ± 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**
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
  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:

- **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.

Pepitic 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 sorcrose 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, embryofetal 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 ≥1/10
- Common ≥1/100 to <1/10
- Uncommon ≥1/1000 to <1/100
- Rare ≥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: diarrhea
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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Version number: NCDS v.2 Revision date: 11 April 2011