INHALEX Respules (Ambroxol hydrochloride)

Composition

Each 2 ml respule contains

Ambroxol Hydrochloride ..................... 15 mg
In an isotonic solution

Dosage Form

Solution for inhalation via a nebulizer

Description

Ambroxol Hydrochloride is also known as hydrochloric acid bromine cyclohexylamine alcohol. Its chemical name is trans-4- cyclohexanol hydrochloride, it is the active metabolite of the expectorants bromhexine and is freely soluble in water

Pharmacology

Pharmacodynamics

Ambroxol is an active N-desmethyl metabolite of the mucolytic bromhexine. Although its mechanism of action has not been fully defined, it may increase the quantity and decrease the viscosity of tracheobronchial secretions. It may also act as an expectorant, increasing mucociliary transport via stimulation of ciliary motility.

Ambroxol may stimulate the synthesis and secretion of pulmonary surfactant; the drug has been referred to as a “surfactant activator”.

The effects of ambroxol in preventing bronchial hyper-reactivity were investigated. Methacholine provocation doses were significantly higher (p <0.01) after ambroxol treatment versus placebo. It was postulated that ambroxol decreased airway hyper-reactivity by either increasing lysophosphatidyl-choline turnover and/or modifying epithelial secretions.

Recent research attributes antioxidative characteristics to ambroxol. Ambroxol has been demonstrated to be a direct scavenger of reactive oxygen metabolites. In an in vitro study using specimens from 46 healthy human volunteers, ambroxol significantly reduced reactive oxygen species (ROS) produced by activated human polymorphonuclear cells (PMN) after 1 hour (p <0.001); after 2 hours, the level was comparable to that of non-activated PMN (p <0.001); the reduction of mononuclear cells mimicked that of PMNs; reduction in the pro-oxidative metabolism of inflammatory cells is another postulated mechanism of action.

Pharmacokinetics

Absorption

Time to peak concentration after oral administration is approximately 2 hours. In a study, it was found that after a single 30 mg oral dose of ambroxol, the mean peak plasma concentration was 88.8 ng/ml.
Bioavailability of ambroxol administered orally is approximately 70-80%. Ambroxol is rapidly absorbed after oral administration.

**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. The distribution half-life of ambroxol is 1.3 hours.

**Metabolism**

15 mg trans-4-cyclohexanol-hydrochloride (ambroxol, NA 872) was administered i.v. and orally to healthy volunteers. The metabolic pattern in urine and plasma was similar for both routes of administration. Biotransformation reactions are straightforward, yielding two major products of phase I reactions identified as 6,8-dibromo-3-(trans-4-hydroxycyclohexyl)-1,2,3,4-tetrahydro-quinazoline and 3,5-dibromo-anthranilic acid. These metabolites as well as the parent compound are also converted to conjugates, predominantly glucuronides.

**Excretion**

Elimination of ambroxol is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours. Excretion is primarily by the kidneys. Renal clearance (rate) is approximately 53 ml/minute; approximately 5-6% of a dose is excreted unchanged in the urine. The elimination half-life of the parent compound is 8.8 hours.

**Indications**

INHALEX Respules are indicated for acute and chronic respiratory tract disease, spasmodic stenosis, abnormal bronchial mucous production, especially bronchial asthma, and emphysema.

INHALEX Respules are also indicated for treatment of secretion disorders in acute and chronic bronchopulmonary infections.

**Dosage And Administration**

- **Adults and Children (Above 5 years of age)**
  
  1 respule (15 mg) twice daily

- **Children (Below 5 years of age)**
  
  Half respule (7.5 mg) twice daily

INHALEX Respules are inhaled with the aid of a nebulizer. They can also be diluted with distilled water in the ratio of 1:1.

**Contraindications**

Hypersensitivity to ambroxol, and in patients with epilepsy.

**Warnings And Precautions**

INHALEX Respules must be administered with precaution to patients suffering from peptic ulcers.

INHALEX Respules should not be allowed as prolonged treatment for protracted illnesses. If the results are not appreciable within a short treatment period, it is advisable to consult the doctor. INHALEX Respules should be used carefully in patients with gastric ulcers.

Care to be taken to avoid contact with eye, skin, serious ingestion or inhalation.

In patients with symptoms of chronic impairment of secretion production or secretion clearance, INHALEX Respules
should be used only when prescribed by a doctor.
In patients with ciliary dyskinesia the benefit of liquefaction of secretions should be carefully weighed against the risk of congestion of secretions.
Concomitant administration of antitussives should be avoided due to the risk of congestion of secretions.

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.

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

Pregnancy
Teratogenic and foetal toxicity studies have shown no harmful effects of INHALEX Respules.

Lactation
INHALEX Respules should not be administered to nursing mothers.

Undesirable Effects

At the recommended doses, INHALEX Respules are well tolerated. Nausea, epigastric distress, headache, and gastrointestinal disorders have rarely been observed.
INHALEX Respules may cause skin, eye or respiratory tract irritation. Ingestion of large doses may cause gastrointestinal tract irritation with decreased motility or constipation, ulceration or bleeding from the stomach or duodenum, and peritonitis. May affect behaviour/central nervous system (tremor, convulsions, ataxia, and somnolence), respiration (dyspnoea, respiratory stimulation), liver, blood (changes in white blood cell count), and the urinary system.
Under individual hypersensitivity to Ambroxol allergic reactions such as skin rash, nettle-rash, and angioneurotic oedema are possible. Under the prolonged administration in large doses pain in epigastrial area, nausea, vomiting can appear.

Gastrointestinal Disorders
Dyspepsia, constipation, nausea, vomiting, diarrhea, excessive salivation, xerostomia and abdominal pain.

Respiratory, Mediastinal and Thoracic Disorders
Rhinorrhea, Oral and pharyngeal hypoaesthesia, dry mouth and dry throat.

Nervous System Disorders
Dysgeusia (eg, changed taste), fatigue.

Immune System Disorders
Anaphylactic reactions including anaphylactic shock.

Skin and Subcutaneous Tissue Disorders
Angioedema, rash, urticaria, contact dermatitis, pruritus and other hypersensitivity.
Anaphylactic reactions and severe cutaneous adverse reactions (SCARs), including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in patients receiving ambroxol.
The risk of anaphylactic reactions and SCARs with ambroxol or bromhexine is low. Frequencies of these side effects are unknown.
Advise your patients that they should stop treatment immediately if symptoms of progressive skin rash occur.
Renal Effects

Dysuria

If case of any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

No information is available on overdosage with INHALEX Respules.

Packaging Information

INHALEX Respules 15mg ........ available as respule of 2 ml

Last Updated: July 2018
Last Reviewed: July 2018

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