MUCOSOLVAN®

30 mg Tablets

ambroxol hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ambroxol hydrochloride .....30 mg

For one scored tablet

Excipient with known effect: lactose
For the full list of excipients, see section List of excipients.

Description
Round, white tablets, both faces flat, with bevelled edges; one face is scored and impressed with '67C' above and below the score: the other face is blank.

CLINICAL PARTICULARS

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

Posology and method of administration
FOR ORAL USE IN ADULTS ONLY

Tablet 30 mg
Adult : 1 tablet 3 times daily.
The therapeutic effect may be enhanced by administering 2 tablets 2 times daily. The tablets should be taken with liquid.
In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen in the course of therapy.
Mucosolvan can be taken with or without food.

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

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), Erythema Multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol hydrochloride. In most cases, these could be explained by the severity of the underlying disease or concomitant administration of another drug. In the early stages of such severe skin reactions, initially only nonspecific flu-like symptoms appear, e.g. fever, arthralgia, runny nose, cough, and sore throat. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, ambroxol hydrochloride treatment should be discontinued immediately and medical advice should be sought as a precaution.

Combining drugs that affect bronchial secretions with antitussives and/or substances that dry up secretions (atropine-like agents) is irrational.

AMBROXOL HYDROCHLORIDE 30 mg tablets may be used in patients with severely impaired hepatic or renal function only after consulting a physician. Like with all drugs that are metabolised by the liver and then eliminated by the renal route, accumulation of ambroxol metabolites generated by the liver can be expected in severe renal failure.

This medicinal product contains lactose. One tablet contains 171 mg of lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction
There are no known clinically relevant interactions with other medicinal products.

Fertiity, pregnancy and lactation

Pregnancy
Ambroxol hydrochloride crosses the placental barrier.

There is no evidence from preclinical studies that ambroxol hydrochloride is teratogenic. As no teratogenic effects have been seen in animals, no malformative effects are expected in humans. To date, substances responsible for malformations in humans have shown to be teratogenic in animals during well-conducted studies in 2 species.

In clinical practice, there are currently no sufficiently relevant data to evaluate a possible malformative or foetotoxic effect of ambroxol hydrochloride when it is administered during pregnancy.

Administration of ambroxol after the 28th week of pregnancy has not caused harmful effects in the foetus.

Consequently, as a precautionary measure, it is preferable to avoid the use of ambroxol hydrochloride during pregnancy, particularly during the first trimester.

Breast-feeding
Animal studies have shown that ambroxol hydrochloride is excreted in breast milk.

Although harmful effects on breast-fed infants are not expected, AMBROXOL HYDROCHLORIDE 30 mg tablets are not recommended for use during breast-feeding.

Fertility
No clinical data on fertility are available.

Preclinical data do not indicate any direct or indirect harmful effects on fertility.

Effects on ability to drive and use machines
Postmarketing surveillance revealed no effects on the ability to drive and use machines with AMBROXOL HYDROCHLORIDE 30 mg tablets.

Studies on the effects on the ability to drive and use machines have not been performed.

Undesirable effects
Side effects are classified using the following frequencies:
• 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

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 generalised exanthematous pustulosis).

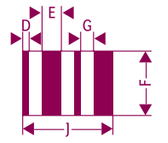
If these reactions occur, treatment must absolutely be discontinued.

Gastrointestinal disorders

• Common: Nausea
• Uncommon: vomiting, dyspepsia, diarrhoea, and abdominal pain.

Nervous system disorders

• Very rare: headache, dizziness.



MASS D 0,5 mm
MASS E 1,5 mm
MASS G 1,0 mm
MASS F 6,0 mm

Example Technical information control code

Overdose
No specific overdose symptoms have been reported in humans.

Based on accidental overdose and/or medication error reports, the observed symptoms are consistent with the known side effects of AMBROXOL HYDROCHLORIDE 30 mg tablets at recommended doses.

Symptomatic treatment is indicated in the event of overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Mucolytics, ATC code: R05CB06.

Mechanism of action

Ambroxol hydrochloride has mucokinetic and expectorant properties.

Due to its effect on secretory cells, it improves bronchial secretion and promotes the production of mucus that is easier to clear. It increases ciliary activity.

The local anaesthetic effect of ambroxol hydrochloride has been observed in the rabbit eye model which may be explained by the sodium channel blocking properties. It was shown *in vitro* that ambroxol hydrochloride blocks cloned neuronal sodium channels. Binding is reversible and concentration-dependent.

These pharmacological features are in accordance the observations in clinical efficacy studies for the treatment with ambroxol hydrochloride of upper respiratory tract symptoms that leads to rapid relief of pain and pain-related discomfort in the ear-nose-trachea region upon inhalation.

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

In clinical studies in patients with sore throat, pharyngeal pain and redness was significantly reduced.

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

Pharmacokinetics properties
Absorption
Immediate-release oral forms of ambroxol hydrochloride are rapidly and completely absorbed, and doses are linear 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 an average of 6.5 hours for the prolonged-release formulation.

The absolute bioavailability after administration of a 30 mg tablet was 79%.

Food has not been found to affect the bioavailability of ambroxol hydrochloride when administered orally.

Distribution
Ambroxol hydrochloride is rapidly and widely distributed from blood to body tissues, with the highest concentration of the drug found in the lungs.

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

In the therapeutic range, the drug is approximately 90% plasma protein-bound.

Biotransformation and elimination
Thirty percent of an orally administered dose is eliminated via first pass metabolism.

Ambroxol hydrochloride is primarily metabolised in the liver by glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose), as well as some minor metabolites.

Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol hydrochloride to dibromanthranilic acid.

Within 3 days of oral administration, approximately 6% of the dose is found in free form, while approximately 26% of the dose is recovered in conjugated form in the urine.

The elimination half-life is approximately 10 hours. No accumulation of the medicinal product has been observed during measurement of the plasma concentration following repeat-dose administration at therapeutic doses.

Total clearance is in the range of 660 mL/min, with renal clearance accounting for approximately 8% of the total clearance following oral administration. It was estimated that approximately 83% of the total dose is excreted in urine after 5 days (radioactivity).

Pharmacokinetics in special patient populations:
In patients with impaired liver function, elimination of ambroxol hydrochloride is reduced, resulting in approximately 1.3 to 2-fold higher plasma levels.

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

Dose adjustment based on sex or age is not necessary.

PHARMACEUTICAL PARTICULARS

List of excipients
Lactose, maize starch, Silica colloidal anhydrous, magnesium stearate

Availability
50 Tablets per blister
Store below 30° C.
Please refer to packaging for information on shelf-life

Manufactured by
Delpharm Reims
10 rue Colonel Charbonneaux
51100 Reims
France

Product License Holder:
In Malaysia:
DKSH Malaysia Sdn Bhd,
B-11-01, The Ascent, Paradigm
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Store in a safe place out of the reach of children!

Opella.