

Proposed CORE SAFETY PROFILE

Mucoangin®: Lozenges, 20 mg

Mucosolvan®: Soft pastille, 15 mg

Tablet, 30 mg

Film-coated tablet, 60 mg

Effervescent tablets, 60 mg

Retard capsule, 75 mg

Granules, 30 mg/3g, 60 mg/3g

Syrup, 15 mg/5ml and 30 mg/5ml

Solution for oral use, 15 mg/2ml and 30 mg/2ml

Solution for inhalation, 15 mg/2ml

Infusion solution concentrate, 1000 mg/50ml

Ampoules, 15 mg/2ml

4.1 Therapeutic indications

Section 4.1 Therapeutic indications is provided for information only. Not all indications may be registered in every country.

Mucoangin® Lozenges, 20 mg:

Pain relief in acute sore throat.

Mucosolvan® infusion solution concentrate, 1000 mg/50ml:

To enhance prenatal lung maturation and as prophylaxis of respiratory distress syndrome in the case of

- imminent premature delivery during the 28th to 34th week of pregnancy
- indicated premature termination of pregnancy during the 28th to 34th week of pregnancy as a result of a foetal or maternal emergency (e.g. rh-incompatibility, diabetes mellitus, EPH gestosis)
- insufficient lung maturation as shown by amniotic tests, even until the 36th week of pregnancy
- premature rupture, if it can be clinically foreseen that the gestation period could be extended by at least 3 days.

Mucosolvan® Ampoules, 15 mg/2 ml:

Treatment of the infant respiratory distress syndrome (IRDS) in premature babies and newborns.

All other formulations:

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

4.3 Contraindications

MUCOSOLVAN® / MUCOANGIN® 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 Special warnings and precautions) the use of the product is contraindicated. >
(only to be included if excipients (carbohydrates) are included in the product that need to be labeled)*

Additionally for Mucosolvan® infusion solution concentrate, 1000 mg/50ml :

MUCOSOLVAN® infusion solution concentrate should not be administered if the patient suffers from convulsions of various aetiology.

4.4 Special warnings and precautions for use

All formulations except for Mucosolvan® infusion solution concentrate, 1000 mg/50ml and Mucosolvan® Ampoules, 15 mg/2 ml:

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 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 can first experience non-specific influenza-like prodromes like e.g. fever, aching body, rhinitis, cough and sore throat. Misled by these 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 hydrochloride discontinued as a precaution.

All formulations except for Mucosolvan® infusion solution concentrate, 1000 mg/50ml and Mucosolvan® Ampoules, 15 mg/2 ml:

In the presence of impaired renal function or severe hepatopathy, Mucosolvan®/Mucoangin® may be used only after consulting a physician. As for any medication with hepatic metabolism followed by renal elimination, accumulation of the metabolites of ambroxol generated in the liver can be expected in the presence of severe renal insufficiency.

Mucosolvan® infusion solution concentrate, 1000 mg/50ml and Mucosolvan® Ampoules, 15 mg/2 ml:

In the presence of impaired renal function or severe hepatopathy Mucosolvan® should be administered with precaution.

As for any medication with hepatic metabolism followed by renal elimination, accumulation of the metabolites of ambroxol generated in the liver can be expected in the presence of severe renal insufficiency.

Additionally for Mucosolvan® infusion solution concentrate, 1000 mg/50ml :

MUCOSOLVAN® infusion solution concentrate is only designed for slow intravenous drip.

Rapid i.v. bolus injections should be avoided, as central nervous reaction cannot be ruled out.

Accidental undiluted bolus administration may cause haemolysis due to the high concentration of active ingredient at the site of injection.

Intra-arterial use should also be avoided, as local oedema and slight cicatrisation around the administration site has been observed in preclinical studies.

All formulations:

< Special warnings regarding the excipients that need to be labeled should be included - if appropriate.>

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant unfavourable interaction with other medications has been reported.

4.6 Pregnancy and Lactation

Only for Mucosolvan® Ampoules, 15 mg/2 ml:

Not applicable.

All formulations except for Mucosolvan® Ampoules, 15 mg/2 ml:

Ambroxol hydrochloride crosses the placental barrier. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Extensive clinical experience after the 28th week of pregnancy has shown no evidence of harmful effects on the foetus.

All formulations except for Mucosolvan® Ampoules, 15 mg/2 ml and Infusion solution concentrate, 1000 mg/50 ml:

Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed.

Especially during the first trimester, the use of MUCOSOLVAN® / MUCOANGIN® is not recommended.

All formulations except for Mucosolvan® Ampoules, 15 mg/2 ml:

Ambroxol hydrochloride is excreted in breast milk.

Although unfavourable effects on breastfed infants would not be expected, MUCOSOLVAN® / MUCOANGIN® is not recommended for use in nursing mothers.

4.7 Effects on ability to drive and use machines

Only for Mucosolvan® Ampoules, 15 mg/2 ml:

Not applicable.

Only for Mucosolvan® Infusion solution concentrate, 1000 mg/50 ml:

There is no evidence for an effect on the ability to drive and use machines.
Studies on the effects on the ability to drive and use machines have not been performed.

However, patients should be advised that they may experience “dizziness”.
Therefore, caution should be recommended when driving a car or operating machinery. If patients experience “dizziness” they should avoid potentially hazardous tasks such as driving or operating machinery.

All other formulations:

There is no evidence for an effect on the ability to drive and use machines.
Studies on the effects on the ability to drive and use machines have not been performed.

4.8 Undesirable effects

Only for Mucosolvan® Infusion solution concentrate, 1000 mg/50 ml:

Immune System Disorders, Skin and subcutaneous tissue disorders and Respiratory, thoracic and mediastinal disorders:

Uncommon: hypersensitivity

Not known: Anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus

Nervous System Disorders:

Common: Headache

Uncommon: Dizziness

Cardiac Disorders:

Common: Tachycardia

Vascular Disorders:

Common: Flushing

Uncommon: Circulatory disorders

Gastro-intestinal disorders:

Very common: Nausea

Common: Vomiting

Uncommon: Diarrhoea and abdominal pain

Not known: Dyspepsia

Only for Mucosolvan® Ampoules, 15 mg/2 ml:

Immune system disorders, Skin and subcutaneous tissue disorders:

Not known: Anaphylactic reactions including anaphylactic shock, angioedema, rash; urticaria, pruritus and other hypersensitivity.

Gastro-intestinal disorders:

Not known: Nausea, vomiting, diarrhoea, dyspepsia and abdominal pain.

Only for Mucoangin® Lozenges, 20 mg:

Immune system disorder, Skin and subcutaneous tissue disorders:

Not known: Anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus and other hypersensitivity.

Nervous system disorders:

Common: Dysgeusia (e.g. changed taste)

Gastro-intestinal disorders and Respiratory, mediastinal and thoracic disorders:

Common: Nausea, oral and pharyngeal hypoaesthesia

Uncommon: Diarrhoea, abdominal pain upper, dyspepsia and dry mouth

Not known: Vomiting and dry throat

All other formulations:

Immune system disorders, Skin and subcutaneous tissue disorders:

Rare: Rash, urticaria

Not known: Anaphylactic reactions including anaphylactic shock, angioedema, pruritus and other hypersensitivity.

Gastro-intestinal disorders:

Common: Nausea

Uncommon: Vomiting, diarrhoea, dyspepsia and abdominal pain.

Additionally for Mucosolvan® Soft pastilles, 15 mg; Mucosolvan® Granules, 15 mg/3g, 30 mg/3g, 60 mg/3g; Mucosolvan® Syrup, 15 mg/5ml and 30 mg/5ml; Mucosolvan® effervescent tablets, 60 mg; Mucosolvan® Solution for oral use, 15 mg/2ml and 30 mg/2ml; Mucosolvan® Solution for inhalation, 15 mg/2ml:

Nervous system disorders:

Common: Dysgeusia (e.g. changed taste)

Gastro-intestinal disorders and Respiratory, mediastinal and thoracic disorders:

Common: Oral and pharyngeal hypoaesthesia

Uncommon: Dry mouth

Not known: Dry throat

4.9 Overdose

No specific overdose symptoms 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 MUCOSOLVAN®/MUCOANGIN® at recommended doses and may need symptomatic treatment.

5.3 Preclinical safety data

Ambroxol hydrochloride has a low index for acute toxicity. In repeat-dose studies, oral doses of 150 mg/kg/day (mouse, 4 weeks), 50 mg/kg/day (rat, 52 and 78 weeks), 40 mg/kg/day (rabbit, 26 weeks) and 10 mg/kg/day (dog, 52 weeks) were the no-observed adverse effect level (NOAEL). No toxicological target organs were detected. Four week intravenous toxicity studies with ambroxol hydrochloride in rats (4, 16 and 64 mg/kg/day) and in dogs (45, 90 and 120 mg/kg/day (infusion 3 h/day)) showed no severe local and systemic toxicity including histopathology. All adverse effects were reversible.

Ambroxol hydrochloride was neither embryotoxic nor teratogenic when tested at oral doses up to 3000 mg/kg/day in rats and up to 200 mg/kg/day in rabbits. The fertility of male and female rats was not affected up to 500 mg/kg/day. The NOAEL in the peri- and post-natal development study was 50 mg/kg/day.

At 500 mg/kg/day, ambroxol hydrochloride was slightly toxic for dams and pups, as shown by a retarded body-weight development and reduced litter size.

Genotoxicity studies *in vitro* (Ames and chromosome aberration test) and *in vivo* (mouse micronucleus test) did not reveal any mutagenic potential of ambroxol hydrochloride.

Ambroxol hydrochloride did not show any tumorigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg/day) and rats (65, 250 and 1000 mg/kg/day) when treated with a dietary admixture for 105 and 116 weeks, respectively.