MUCOSOLVAN® 24 Hours

SANOFI

Composition
1 sustained-release capsule contains 75 mg
trans-4-[(2-amino-3,5-dibromo-benzyl) amino] cyclohexanol hydrochloride(= ambroxol hydorchloride)

Excipients:
Crospovidone collidon CL, carnauba wax, stearyl alcohol, magnesium stearate
Hard gelatin capsule composition: Gelatin, titanium dioxide, red iron oxide, yellow iron oxide
White printing ink composition: Shellac, isopropyl alcohol, n-Butyl alcohol, propylene glycol, titanium dioxide

Description
Oblong hard gelatin capsules consisting of red opaque cap and an orange opaque body; the cap is printed with "MUC 01" in white, the body is printed with the BI Company symbol.
Capsule contents : round, yellowish white-pallets with a smooth, shiny surface, mixed with a small quantity of powder.

Dimensions:
Capsule size : 2
Diameter of capsule cap : 6.0-6.4mm
Length of capsule : 17.4 – 18.4mm

Properties
Preclinically, ambroxol hydrochloride, the active ingredient of MUCOSOLVAN, has been shown to increase respiratory tract secretion. It enhances pulmonary surfactant production and stimulates ciliary activity. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and eases cough.

In patients suffering from COPD, long-term treatment (6 months) with Mucosolvan® (Mucosolvan® Retard Capsule 75 mg) resulted in a significant reduction of exacerbations that became evident after 2 months of treatment. Patients in the Mucosolvan® treatment group lost significantly fewer days through illness and had fewer days when they needed antibiotic therapy. Treatment with Mucosolvan® Retard also induced a statistically significant improvement of symptoms (difficulty of expectoration, cough, dyspnea, auscultatory signs) compared with placebo.

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

Pharmacokinetics
Absorption:
Absorption of all immediate release oral forms of ambroxol hydrochloride is rapid and complete, with dose linearity 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 a median of 6.5 hours of the slow release formulation. The absolute bioavailablility after a 30 mg tablet was found to be 79%. The slow release capsule showed a relative availability of 95% (dose-normalized) in comparison to a daily dose of 60 mg (30 mg twice daily) administered as immediate-release tablet.

Distribution:
In the therapeutic range plasma protein binding was found to be approximately 90%. Distribution of ambroxol hydrochloride from blood to tissue is rapid and pronounced, with the highest concentration of the active substance found in the lungs. The volume of distribution following oral administration was estimated to be 552L.

Metabolism and elimination:
About 30% of an orally administered dose is eliminated via first pass metabolism. Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol. Ambroxol hydrochloride is metabolized primarily in the liver by glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose) aside from some minor metabolites.
Ambroxol hydrochloride is eliminated with a terminal elimination half-life of approximately 10 hours. Total clearance is in the range of 660 ml/min, with renal clearance accounting for approximately 83% of the total clearance.

Pharmacokinetics in special populations:
In patients with hepatic dysfunction elimination of ambroxol hydrochloride is reduced, resulting in approximately 1.3 to 2-fold higher plasma levels.
Due to the high therapeutic range of ambroxol hydrochloride, dose adjustments are not necessary.

Others:
Age and gender were not found to affect the pharmacokinetics of ambroxol hydrochloride to a clinically relevant extent and thus there is no necessity for adjustment of dosage regimens.
Food was not found to influence the bioavailability of ambroxol hydrochloride.

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

Dosage and Administration
Adult : 1 sustained-release capsule once daily.
The capsules should not be opened or chewed, but swallowed whole with ample liquid. The "carrier pellets" which are occasionally present in the stools have released the active substance during their passage through the digestive system and are therefore without significance.

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
MUCOSOLVAN 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.

Special warnings and precautions
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 may first experience 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 discontinued as a precaution.

In the presence of impaired renal function MUCOSOLVAN® may be used only after consulting a physician.

Interactions
No clinically relevant unfavourable interaction with other medications have been reported

Fertility, pregnancy and Lactation

Pregnancy
Ambroxol hydrochloride crosses the placental barrier. Nonclinical 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. Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed. Especially during the first trimester, the use of MUCOSOLVAN is not recommended.

Lactation
Ambroxol hydrochloride is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, MUCOSOLVAN is not recommended for use in nursing mothers.

Fertility
Nonclinical studies do not indicate direct or indirect harmful effects with respect to fertility.

Effects on ability to drive and use machines
There is no evidence from postmarketing data 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.

Side Effects

Gastro-intestinal Disorders:

Dyspepsia, nausea, vomiting, diarrhoea and abdominal pain.

Immune System Disorders, Skin and Subcutaneous Tissue Disorders:

Anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus, and other hypersensitivity

Overdosage
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 at recommended doses and may need symptomatic treatment.

Availability
10's & 50's
sustained-release capsules 75 mg

Store in a safe place out of reach of children!
Store below 30° C.
Please refer to packaging for information on shelf-life

Manufactured by
Boehringer Ingelheim
Pharma GmbH & Co. KG
Birkendorfer Strasse 65,
D-88379 Biberach, Germany

Product Registration Holder
In Malaysia:
sanofi-aventis (Malaysia)
Sdn Bhd (334110-P)
Unit TB-18-1, Level 18, Tower B, Plaza 33,
No. 1 Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya
Selangor Darul Ehsan, Malaysia

Product Registrant
In Singapore:
sanofi-aventis Singapore Pte Ltd
38 Beach Road #18-11
Singapore 189767

Date of revision: May 2017

Store in a safe place out of the reach of children!

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Special warnings and precautions
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Effects on ability to drive and use machines
There is no evidence from postmarketing data 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.

Side Effects

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

Dyspepsia, nausea, vomiting, diarrhoea and abdominal pain, oral and pharyngeal hypoaesthesia, dry mouth and dry throat.

Nervous system disorders:

Dysgeusia (e.g. changed taste)

Immune System Disorders, Skin and Subcutaneous Tissue Disorders:

Anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus, and other hypersensitivity

Overdosage
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 at recommended doses and may need symptomatic treatment.

317424-01

Distribution:
In the therapeutic range plasma protein binding was found to be approximately 90%. Distribution of ambroxol hydrochloride from blood to tissue is rapid and pronounced, with the highest concentration of the active substance found in the lungs. The volume of distribution following oral administration was estimated to be 552L.

Metabolism and elimination:
About 30% of an orally administered dose is eliminated via first pass metabolism.
Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol. Ambroxol hydrochloride is metabolized primarily in the liver by glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose) aside from some minor metabolites. Ambroxol hydrochloride is eliminated with a terminal elimination half-life of approximately 10 hours. Total clearance is in the range of 660 ml/min, with renal clearance accounting for approximately 83% of the total clearance.

Pharmacokinetics in special populations:
In patients with hepatic dysfunction elimination of ambroxol hydrochloride is reduced, resulting in approximately 1.3 to 2-fold higher plasma levels.
Due to the high therapeutic range of ambroxol hydrochloride, dose adjustments are not necessary.

Others:
Age and gender were not found to affect the pharmacokinetics of ambroxol hydrochloride to a clinically relevant extent and thus there is no necessity for adjustment of dosage regimens. Food was not found to influence the bioavailability of ambroxol hydrochloride.

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

Dosage and Administration
Liquid 30 mg/ 5 ml
Adults and children over 12 yrs:
10 ml 2 times daily.
This regimen is suitable for the therapy of acute respiratory tract disorders and for the initial treatment of chronic conditions up to 14 days.

Children 6 - 12 yrs:	5 ml 2 - 3 times daily.
Chirdren 2 - 5 yrs:	2.5 ml 3 times daily.
Children 1 - 2 yrs:	2.5 ml 2 times daily.

This dosage regimen is for initial treatment; the dosage may be halved after 14 days.

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
MUCOSOLVAN 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.

MUCOSOLVAN

SANOFI

Composition
5 ml liquid contains 30 mg
trans-4-[(2-amino-3,5-dibromo-benzyl)amino] cyclohexanol hydrochloride(= ambroxol hydrochloride)

Excipients
Liquid 30 mg:
hydroxyethylcellulose, benzoic acid, sucralose, strawberry cream aroma, vanilla flavour, water purified

Description
Clear or almost clear, colourless elixir

Properties
Preclinically, ambroxol hydrochloride, the active ingredient of MUCOSOLVAN, has been shown to increase respiratory tract secretion. It enhances pulmonary surfactant production and stimulates ciliary activity. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and eases cough.

In patients suffering from COPD, long-term treatment (6 months) with Mucosolvan® (Mucosolvan® Retard Capsule 75 mg) resulted in a significant reduction of exacerbations that became evident after 2 months of treatment. Patients in the Mucosolvan® treatment group lost significantly fewer days through illness and had fewer days when they needed antibiotic therapy. Treatment with Mucosolvan® Retard also induced a statistically significant improvement of symptoms (difficulty of expectoration, cough, dyspnea, auscultatory signs) compared with placebo.

A 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 was reversible and concentration-dependent.

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 antibiotic concentrations (amoxicilline, cefuroxime, erythromycin) in bronchopulmonary secretions and in the sputum are increased.

Pharmacokinetics
Absorption:
Absorption of all immediate release oral forms of ambroxol hydrochloride is rapid and complete, with dose linearity 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 a median of 6.5 hours of the slow release formulation. The absolute bioavailablility after a 30 mg tablet was found to be 79%. The slow release capsule showed a relative availability of 95% (dose-normalized) in comparison to a daily dose of 60 mg (30 mg twice daily) administered as immediate-release tablet.

Availability
Liquid 30 mg/5 ml. 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:
sanofi-aventis (Malaysia)
Sdn Bhd (334110-P)
Unit TB-18-1, Level 18, Tower B,
Plaza 33,
No. 1 Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya
Selangor Darul Ehsan, Malaysia

In Singapore:
sanofi-aventis Singapore Pte Ltd
38 Beach Road #18-11
Singapore 189767

Store in a safe place out of the reach of children!

317424-01

MUCOSOLVAN®

SANOFI

30 mg Tablets

ambroxol hydrochloride

Composition
1 tablet contains..... 30 mg
trans-4-[(2-amino-3,5-dibromo-benzyl)amino] cyclohexanol hydrochloride (= ambroxol hydrochloride)

Excipients:
Lactose monohydrate, maize starch dried, silicia colloidal anhydrous, magnesium stearate

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

Properties
Preclinically, ambroxol hydrochloride, the active ingredient of MUCOSOLVAN, has been shown to increase respiratory tract secretion. It enhances pulmonary surfactant production and stimulates ciliary activity. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and eases cough.

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Metabolism and elimination:
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Others:
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Food was not found to influence the bioavailability of ambroxol hydrochloride.

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

Dosage and Administration
Tablet 30 mg
Adult : 1 tablet 3 times daily.

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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
MUCOSOLVAN 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.

Special warnings and precautions
MUCOSOLVAN tablets (30mg): One tablet contains 171 mg lactose resulting in 684 mg lactose per maximum recommended daily dose (120 mg). Patients with rare hereditary condition of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 may first experience 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 discontinued as a precaution.

In the presence of impaired renal function MUCOSOLVAN® may be used only after consulting a physician.

Interactions
No clinically relevant unfavourable interaction with other medications have been reported

Fertiity, pregnancy and lactation
Pregnancy
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Lactation
Ambroxol hydrochloride is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, MUCOSOLVAN is not recommended for use in nursing mothers.

Fertility
Nonclinical studies do not indicate direct or indirect harmful effects with respect to fertility.

Effects on ability to drive and use machines
There is no evidence from postmarketing data 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.

Side Effects
Gastro-intestinal Disorders:
Dyspepsia, nausea, vomiting, diarrhoea and abdominal pain.

Immune System Disorders, Skin and Subcutaneous Tissue Disorders:
Anaphylactic reactions including anaphylactic shock, angioedema, rash, urticaria, pruritus, and other hypersensitivity

Overdosage
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 at recommended doses and may need symptomatic treatment.

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

Manufactured by
PT. Boehringer Ingelheim Indonesia
Jl Lawang Gintung No 89
Bogor 16133
Indonesia

Product Registration Holder in Malaysia:
sanofi-aventis (Malaysia) Sdn Bhd (334110-P)
Unit TB-18-1, Level 18, Tower B, Plaza 33,
No. 1 Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya
Selangor Darul Ehsan, Malaysia

Product Registrant in Singapore:
sanofi-aventis Singapore Pte Ltd
38 Beach Road #18-11
Singapore 189767

Date of revision: May 2017

Store in a safe place out of the reach of children!

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