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Digital · Packaging · Development

Opella.

File information

GMID code:	662272
Plant PM code:	10053297
Second Plant PM code:	324604-06
Version of artwork:	V1
PM type:	PI
Market:	XR
Format:	270 x 210 mm
Issue date of artwork:	07/Feb/2025
Print colors:	Black
Number of print colors:	1
Used font:	Gotham
Min. font size:	9 pt

Technical colors

Diecut-Legendcase		Free area		Glue points	

ADDITIONAL REQUIREMENT OF PACKAGING LINE

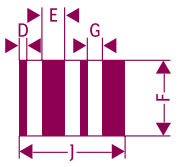
Description : PI MUCOSOLVAN 600MG/+ SYR BT1 M36 XR

Dimension : 210 x 270 mm

No. of code : 136

Ref. drawing : PR8 **Issue date of TD:** 28/01/2025

Leaflet "double-glued": For security reason, the n° of page must be printed at the bottom of each page as indicated on the TD.
Notice "double collée": pour des raisons de sécurité, le numéro de la page doit être imprimée en bas de chaque page comme c'est indiquée sur la donnée technique.



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

Contraindications
Hypersensitivity to the active substance (ambroxol hydrochloride) or any of the other excipients listed.
Mucosolvan cough syrup 30 mg/5 ml must not be used in children under 2 years of age except on medical advice.

Special warnings and precautions
Very rare cases of chronically associated severe skin impairments such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported. 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.

In patients with impaired bronchial motility and copious secretions (as seen, for instance, in the rare and malignant primary ciliary dyskinesia), Mucosolvan cough syrup 30 mg/5 ml must be used with caution because of the risk that secretions may accumulate.

In patients with impaired kidney function or severe liver disease, Mucosolvan should not be used except on medical advice. With ambroxol, as with any medicine that is metabolized hepatically and excreted renally, accumulation of the metabolites of ambroxol which are formed in the liver can be expected to occur in patients with severe renal failure.
Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

In babies under 4 weeks of age this medicine should be used with caution; in particular if the baby is given other medicines that contain propylene glycol or alcohol.

Interactions
If Mucosolvan is used in combination with antitussives in patients with pre-existing respiratory diseases such as cystic fibrosis or bronchiectasis who are affected by mucus hypersecretion, a reduced cough reflex may lead to (serious) accumulation of mucus.

Fertility, pregnancy and lactation

Pregnancy
Ambroxol hydrochloride crosses the placental barrier. Non-clinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, labour and delivery or postnatal development. Extensive clinical experience after the 28th week of pregnancy has shown no evidence of harmful effects on the foetus. However, the usual precautions concerning the administration of any medicine during pregnancy should be observed. The use of Mucosolvan is not recommended during the first trimester of pregnancy in particular.

Breast-feeding
Ambroxol has been shown to pass into breast milk in animal studies. Use while breast-feeding is not recommended.

Fertility
Non-clinical studies do not indicate direct or indirect harmful effects with respect to fertility.

32604-06

MUCOSOLVAN®

Opella.

Composition
5 ml of the solution contains
30 mg ambroxol hydrochloride

Excipients with known effect:
This medicine contains 2.5 mg benzoic acid and 28.75 mg propylene glycol (ingredient of the flavours) in 5 ml of solution.

List of excipients
Benzoic acid, hydroxyethylcellulose, sucralose, flavouring agents (containing propylene glycol), purified water.

Description
Oral solution
Colourless liquid with a fruity odour.

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.

Antiviral properties in in vitro studies and in animal models:
In in vitro studies in human tracheal epithelial cells a reduction of rhinovirus (RV14) replication has been observed. In a mouse airway model, a reduction of Influenza A virus replication was observed with ambroxol pretreatment.

Pharmacokinetics
<u>Absorption:</u>
Absorption of immediate release oral dosage forms of ambroxol hydrochloride is fast and complete, with dose linearity in the therapeutic range. Maximum plasma levels are reached within 1 to 2.5 hours after administration of the **immediate-release formulation and after a**

median of 6.5 hours after administration of the slow-release formulation.
The absolute bioavailablility after ingesting a 30 mg tablet is 79%. The prolonged-release capsule showed a relative availability of 95% (dose-normalized) in comparison to tablets with unchanged active substance release (60 mg daily dose, 30 mg twice daily).

Food was not found to have any effect on the bioavailability of ambroxol hydrochloride.

Distribution:
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 estimated volume of distribution after oral administration is 552 litres.
In the therapeutic range plasma protein binding is was found to be approximately 90%.

Metabolism:
About 30% of the orally administered dose is eliminated via first-pass metabolism. Ambroxol hydrochloride is primarily metabolized in the liver through glucuronidation and cleavage to dibromanthranilic acid (approx. 10% of the dose). Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol hydrochloride to dibromoanthranilic acid.

Elimination:
After 3 days of oral administration, ambroxol hydrochloride is eliminated renally, approx. 6% unchanged and approx. 26% in the form of its conjugates.
The terminal elimination half-life of ambroxol hydrochloride is about 10 hours. Total clearance is in the range of 660 ml/min, with renal clearance accounting for approx. 8% of the total clearance.

After 5 days an estimated 83% of total dose (radioactively marked) is eliminated with the urine.

Special patient groups:
The elimination of ambroxol hydrochloride is reduced in patients with impaired liver function, resulting in plasma levels approx. 1.3 to 2 times higher.
Due to the high therapeutic range of active substance, a dose adjustment is not necessary.

Age and gender were not found to affect the pharmacokinetics of ambroxol hydrochloride to a clinically relevant degree. Therefore, deviating from the recommended dose is not necessary.

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.
Children 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.

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

The following categories are normally used when reporting the frequencies of side effects:

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:	Frequency 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 skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP).

Nervous system disorders
Common: Dysgeusia (e.g. changed taste)

Gastrointestinal disorders
Common: Nausea, oral hypoaesthesia
Uncommon: Vomiting, diarrhoea, dyspepsia, abdominal pain, dry mouth
Rare: Dry throat
Very rare: Sialorrhoea

Respiratory, thoracic and mediastinal disorders
Common: Pharyngeal hypoaesthesia
Not known: Dyspnoea (as a symptom of a hypersensitivity reaction)

General disorders and administration site conditions
Uncommon: Fever, mucous membrane reactions

Overdosage
No specific symptoms of overdose have been reported to date. The symptoms observed in cases of accidental overdose or medication error are consistent with the known side effects at the recommended dose and may require symptomatic treatment.

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

Date of revision:
July 2023
(CCDS V1 based on Germany SmPC Dec 2019)

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

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