

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Lysopadol 17.86 mg/ml Oromucosal Spray, Solution

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One actuation of the spray contains 2.5 mg of ambroxol hydrochloride.

One ml of the spray contains 17.86 mg of ambroxol hydrochloride.

Excipient(s) with known effect:

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose (4 actuations) and very small amounts of propylene glycol.

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Oromucosal spray, solution

Clear and almost colourless solution.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

Pain relief in acute sore throat for adults and children over 12 years of age.

#### 4.2 Posology and method of administration

##### Posology

Adults and children over 12 years of age: one dose of 10 mg (4 actuations) to be sprayed into the back of the throat up to 6 times per day.

Lysopadol 17.86 mg/ml Oromucosal Spray can be used for up to 3 days. In case of persistent symptoms or high fever, the patient should consult a doctor.

##### *Paediatric population*

Lysopadol 17.86 mg/ml Oromucosal Spray should not be used in children under 12 years of age (see section 4.4).

##### Method of administration

Oromucosal use

Prior to use, the pump should be actuated 5 times so that an even spray mist is released. After not having used the spray for a long time, the pump should be actuated once before applying the product again. For application the spray bottle should be used in an upright position with the nozzle targeted at the back of the throat whilst pushing down the pump head completely.

#### 4.3 Contraindications

Hypersensitivity to the active substance (ambroxol) or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Lysopadol 17.86 mg/ml Oromucosal Spray can be used for up to 3 days. If symptoms worsen or still persist after 3 days or if the patient has a high fever, a doctor should be consulted.

There have been reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol hydrochloride. 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.

Dyspnoea may be observed in the context of an underlying disease e.g. swollen throat. Local allergic reactions (see section 4.8: angioneurotic oedema) may also cause dyspnoea. The local anaesthetic properties of ambroxol may contribute to an altered perception in the pharyngeal space (see section 4.8: oral and pharyngeal hypoaesthesia).

Lysopadol 17.86 mg/ml Oromucosal Spray is not suitable for the treatment of oral ulcers. In such a case medical advice should be sought.

In the presence of impaired renal function or severe hepatopathy, Lysopadol 17.86 mg/ml Oromucosal Spray 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.

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose (4 actuations).

This product contains propylene glycol which may cause mucosal irritation.

### Paediatric population

Lysopadol 17.86 mg/ml Oromucosal Spray should not be used in children under 12 years of age.

## 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 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, 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 Lysopadol 17.86 mg/ml Oromucosal Spray is not recommended.

### Breastfeeding:

Ambroxol hydrochloride is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, Lysopadol 17.86 mg/ml Oromucosal Spray is not recommended for use in nursing mothers.

### Fertility:

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

## 4.7 Effects on ability to drive and use machines

There is no evidence from postmarketing data for an effect on 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

Frequency estimation based on a database of clinical trials:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data). This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than uncommon (3/1226), but might be lower. A precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 1226 patients.

### 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 generalized exanthematous pustulosis).

As generally observed for allergies, the severity of allergic reactions may increase if the patient is again exposed to the same substance (see section 4.3).

### Nervous system disorders

Common: dysgeusia (e.g. changed taste)

### Gastrointestinal disorders and Respiratory, mediastinal and thoracic disorders

Common: oral and pharyngeal hypoaesthesia (see section 4.4), nausea

Uncommon: upper abdominal pain, dyspepsia, dry mouth

Rare: diarrhoea, dry throat

Not known: vomiting

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## 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 Lysopadol at recommended doses and may need symptomatic treatment.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Throat preparations (Anaesthetics, local)

ATC code: R02AD05

A local anaesthetic effect of ambroxol hydrochloride has been observed in the rabbit eye model and is likely to result from sodium channel blocking properties: ambroxol hydrochloride blocks hyperpolarised cloned neuronal voltage-gated sodium channels in vitro; binding was reversible and concentration-dependent.

This property is in accordance with the ancillary observations of a pain relief when using inhaled ambroxol hydrochloride in other diseases of the upper respiratory tract.

Lysopadol 17.86 mg/ml Oromucosal Spray acts locally on the oral and pharyngeal mucosa.

Clinical studies performed with Ambroxol lozenges (containing 20 mg ambroxol hydrochloride) confirmed the pain relieving effects in patients with sore throat due to an acute viral pharyngitis.

Except one, clinical trials have shown an onset of action which can be experienced within 20 minutes at the latest. The effect will last for at least three hours.

A single application (4 actuations) of Lysopadol 17.86 mg/ml Oromucosal Spray has also been shown to demonstrate a clinically relevant reduction in the pain associated with sore throat for at least three hours, with the first effect being observed after 15 minutes.

In vitro, ambroxol hydrochloride seems to exert an anti-inflammatory effect. Cytokine release from blood mononuclear and polymorphonuclear cells but also from tissue-bound mononuclear and polymorphonuclear cells was found to be significantly reduced by ambroxol hydrochloride in vitro.

In clinical trials, Ambroxol lozenges (containing 20 mg ambroxol hydrochloride) have been shown to reduce redness in sore throat significantly.

Also Lysopadol 17.86 mg/ml Oromucosal Spray shows a significant reduction of pharyngeal redness compared to placebo.

## 5.2 Pharmacokinetic properties

### 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 for the slow release formulation.

The absolute bioavailability 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.

Due to the additional absorption via the oral mucosa, administration of lozenge results in an approximately 25% (90% confidence interval = 116-134%) increase in total exposure compared to syrup formulation.

The increased exposure does not negatively affect ambroxol hydrochloride pharmacodynamics in the proposed indication.

### 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 volume of distribution following oral administration was estimated to be 552 L. In the therapeutic range, plasma protein binding was found to be approximately 90%.

### Biotransformation and elimination:

About 30% of an orally administered dose is eliminated via first pass metabolism.

Ambroxol hydrochloride is primarily metabolized in the liver by glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose) aside from 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 a conjugated form in the urine.

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.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Citric acid monohydrate  
Disodium phosphate dihydrate  
Polysorbate 20  
Sucralose  
Cooling flavour (contains propylene glycol)  
Eucalyptus-Menthol flavour (contains propylene glycol)  
Ethanol  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

27 months  
After first opening this medicine can be used for 6 months.

### **6.4 Special precautions for storage**

Do not store above 30° C.  
For storage conditions after first opening of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

Amber glass bottle (type III) with metered dose pump and throat adapter (consisting of different plastic materials).  
Pack size: 20 ml, 30 ml

## **6.6 Special precautions for disposal and other handling**

Prior to use, the pump should be actuated 5 times so that an even spray mist is released. After not having used the spray for a long time, the pump should be actuated once before applying the product again.

For application the spray bottle should be used in an upright position with the nozzle targeted at the back of the throat whilst pushing down the pump head completely.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Sanofi-Aventis Ireland Ltd  
T/A SANOFI  
Citywest Business Campus  
Dublin 24  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0540/186/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 14th February 2014

## **10 DATE OF REVISION OF THE TEXT**

August 2017