Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lysopadol Lemon 20 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One lozenge contains 20 mg of ambroxol hydrochloride.

Excipient(s) with known effect:
Each lozenge contains 1.37 g sorbitol (E420) and 6.3 mg sucrose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lozenge
Round, white tablet, both sides flat with bevelled edges

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pain relief in acute sore throat.

4.2 Posology and method of administration

Posology
Adults and children over 12 years of age: up to 6 lozenges to be sucked per day, with a maximum of 1 lozenge per dose.

Lysopadol Lemon 20 mg Lozenges 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 Lemon 20 mg Lozenges should not be used in children under 12 years of age.

Method of administration
Oromucosal use.

4.3 Contraindications

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

Patients with fructose intolerance should not receive Lysopadol Lemon 20 mg Lozenges since they contain significant amounts of sorbitol.

4.4 Special warnings and precautions for use

Lysopadol Lemon 20 mg Lozenges 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 Lemon 20 mg Lozenges are 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 Lemon 20 mg Lozenges 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 product contains 8.2 g of sorbitol per maximum recommended daily dose (1.37 g per lozenge) and 37.8 mg of sucrose per maximum recommended daily dose (6.3 mg per lozenge). Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Paediatric population
Lysopadol Lemon 20 mg Lozenges 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. 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 28^{th} 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 Lemon 20 mg Lozenges is not recommended.

Breastfeeding
Ambroxol hydrochloride is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, Lysopadol Lemon 20 mg Lozenges are not recommended for use in nursing mothers.

Fertility
Nonclinical 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 post-marketing 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 (≥ 1/10)

Common (≥ 1/100 and < 1/10)
Uncommon (≥ 1/1,000 and < 1/100)
Rare (≥ 1/10,000 and < 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: diarrhoea, upper abdominal pain, dyspepsia, dry mouth
Rare: 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; e-mail: 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 Lemon 20 mg Lozenges at recommended doses and may need symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Throat preparations (Anaesthetics, local).
ATC code: R02AD

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 Lemon 20 mg Lozenges act locally on the oral and pharyngeal mucosa.

Clinical studies confirmed the pain relieving effects of Lysopadol Lemon 20 mg Lozenges 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.

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, Lysopadol Lemon 20 mg Lozenges have been shown to reduce redness in sore throat significantly.

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 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 and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lemon flavour (containing sucrose)
Frescofort flavour
Sorbitol (E420)
Sucralose
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/Aluminium blister.
Pack sizes: 12, 18, 24, 30, 36, 42, 48 lozenges / package.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0540/187/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st June 2012

Date of last renewal: 9th March 2017

10 DATE OF REVISION OF THE TEXT

June 2018