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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Trachisan 8 mg, lozenges
Engelhard Arzneimittel GmbH & Co. KG, Germany

lidocaine (as hydrochloride monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/926/01/MR
Registration number in the Netherlands: RVG 30619

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Pharmacotherapeutic group:	anesthetics, local
ATC code:	R02AD02
Route of administration:	oropharyngeal
Therapeutic indication:	short-term local treatment of pain associated with sore throat in non-purulent infections.
Prescription status:	OTC
Date of authorisation in NL:	24 June 2004
Concerned Member States:	Mutual recognition procedure with CY, CZ, EE, EL, LT, LV, PL and SI
Application type/legal basis:	Directive 2001/83/EC, Article 10(a)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Trachisan 8 mg, lozenges, from Engelhard Arzneimittel GmbH & Co. KG, Germany. The date of authorisation was on 24 June 2004 in the Netherlands. The product is indicated for short-term local treatment of pain associated with sore throat in non-purulent infections.

A comprehensive description of the indications and posology is given in the SPC.

Lidocaine hydrochloride is a local anaesthetic of the amide type. It blocks impulse conduction along sensitive nerve fibres at a local administration site and is reversible. This results in a decreased sensitivity to pain, followed by a decreased sensibility to cold, warmth and touch. In addition, lidocaine has a weak anti-inflammatory and parasympatholytic effect. In contrast to most other local anaesthetics lidocaine does not possess a vasodilative effect.

Lidocaine preparations are widely used as topcial anaesthetic in the mouth, nose, trachea-bronchial tree, oesophagus, and genito-urinary tract. In the Netherlands, Trachitol®, containing 1 mg lidocaine hydrochloride per lozenge, is indicated for sore throat. Also Xylocaine® (a viscous oral solution containing 2% lidocaine), containing the ingredient lidocaine hydrochloride 20 mg/ml, is indicated for stomatitis and pharyngitis and the dosing advice is maximal 5-10 ml six times per day.

The marketing authorisation is granted based on article 10a (well-established medicinal use) of Directive 2001/83/EC. A well-established use application does not require submission of the results of preclinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘’Medicinal use’’ does not exclusively mean ‘’use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use.

In support of this application, the MAH submitted, besides bibliographic references, a pharmacokinetic study, a dose-finding study and a placebo-controlled efficacy study. Following approval in the Netherlands, an additional placebo-controlled trial was submitted to confirm the results of the first placebo-controlled efficacy study.

No new preclinical studies were conducted, which is acceptable for this well-established use application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is lidocaine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Lidicaine hydrochloride is a white crystalline powder that is freely soluble in water, soluble in alcohol and chloroform and insoluble in ether. Lidocaine hydrochloride has no chiral centre. No polymorphism is known.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with the additional requirements according to the CEP for the residual solvent acetone and for impurities detected by a separate HPLC-analysis method. Batch analytical data demonstrating compliance with this specification have been provided for 4 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. Based on the data submitted, a retest period could be granted of 2 years when stored not above 25°C in double PE bags.

** Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Trachisan 8 mg, lozenges contain as active substance of 8 mg of lidocaine hydrochloride (as monohydrate). The lozenges are white, round, flat and with bevelled edges.

The tablets are packed in PVC aluminium foil. The blisters are packed in carton boxes.

The excipients are: sorbitol, peppermint oil and magnesium stearate.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Packaging is usual and suitable for the product at issue.

The objective was to develop a product that is equal to similar products that are already on the market.

Excipients
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 production scale batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for lozenges in the Ph.Eur. and includes tests for parameter, appearance, diameter, height, average weight, uniformity of mass, disintegration, hardness, friability, water content, identification, assay, uniformity of content, related substances and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data 2 pilot scale batches and 1 production scale batches from the proposed production site(s) has been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are*: "Do not store above 25° C." "Do not refrigerate or freeze."* and *"Store in the original package."*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

The pharmacology, pharmacokinetics and toxicology of lidocaine are sufficiently known and lidocaine containing products have been marketed in many countries for many years. Although the dossier contains only limited preclinical data to directly support the safety of Trachisan 8 mg, registration can be granted from a preclinical point of view based on the extensive clinical experience with lidocaine.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of lidocaine hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Besides bibliographic references, three studies with Trachisan 8 mg, lozenges, were submitted. Following approval in the Netherlands, the MAH submitted an additional placebo-controlled trial.

The MEB has been assured that the clinical studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Pharmacokinetics

One study was submitted in which the pharmacokinetics of lidocaine after single dose and at steady state was investigated after administration of lidocaine lozenges 8 mg, every 2 hours. After single dosing, lidocaine is rapidly absorbed, with peak plasma levels at 0.3 hours. At steady state, peak plasma levels (45.4 ± 15.0 ng/ml) are only ca. 10% higher, although the trough levels were more than half of the peak plasma level. In addition, AUC values were similar, indicating no accumulation. The proposed dosage recommendations for 8 mg lozenges are justified by the presented pharmacokinetic data. Additional pharmacokinetic data were literature based.

Clinical studies

Dose finding study

In one double–blind, placebo-controlled dose finding trial (Phase II) performed in 134 patients with moderate to severe (> 40 mm on a VAS) pharyngeal pain as a symptom of acute pharyngitis three dosage of lidocaine, 2 mg (48 patients), 4 mg (31 patients) or 8 mg (26 patients) were administered as a single dose and compared with placebo (27 patients). The primary endpoint was the AUC of Pain Intensity Difference (PID) 0-2 hours after administration measured on a 100 mm visual analogue scale (VAS). The means of AUC of PID reveal a clinically distinct dose relationship. The best efficacy could be detected under 8 mg lidocaine 90 minutes post single dose although the differences between the four groups did not reach statistical significance.

Efficacy studies

One randomised double blind placebo-controlled trial was carried out evaluating the efficacy and tolerability of lidocaine 8 mg lozenges in 160 subjects with moderate to severe (> 60 mm on a visual analogue scale (VAS) for less than 72 hours) pharyngeal pain due to an acute (non-bacterial) pharyngitis. A maximum of six lozenges was allowed over a period of 24 hours with a dose interval of 2 hours. The primary endpoints were the AUC of Pain Intensity over 0-2 hours after administration and the VAS for pain relief after the last lozenge was sucked before returning to the clinician for 48-hours.

Table 1. AUC of VAS Pain

	Geometric mean (SD)			
	Placebo n=80	Lignocaine n=80	Ratio (%)	CI95%
AUC (0-2h)(mm.h)	135 (1.20)	105 (1.53)	76.7	68.2-86.2
AUC (0-48h)(mm.h)	2476 (1.65)	1742 (1.89)	69.3	56.0-85.6

AUC Area under the curve
VAS Visual analog scale 0-100 mm.

Results with respect to the secondary endpoints (onset of ‘meaningful’ and ‘complete’ pain relief, number of subjects discontinuing due to lack of efficacy, global assessment of efficacy by subject and the number of tablets administered) confirm the results for the primary endpoint.

With respect to the experienced adverse events, no differences were observed between the active and the placebo group. The most frequently reported adverse events were headache (6.3% vs 6.3% for placebo and lidocaine respectively), hypoesthesia (0.0% vs. 3.8%), nausea (1.3% vs 5.0%), sore throat (0% vs. 2.5% and voice alteration (1.3% vs. 2.5%).

An additional single centre, randomised, double-blind, placebo-controlled parallel group study was conducted in 240 patients with an acute sore throat not requiring treatment with antibiotics. The study covered a treatment phase of 2 days and was divided into 2 phases: 2-hour laboratory phase and a 2-day out-patient phase.

Primary variable was AUC_{0h-2h} of patient's self-assessment of pain intensity (VAS) The VAS was assessed 15 minutes before the gift and 0, 10, 20, 30, 40, 60 80, 100 and 120 minutes after the gift. In addition PID was scored at 4, 6, 24 and 48 hours.

Efficacy data demonstrated statistically significant differences between lidocaine 8 mg lozenges and placebo: pain intensity reduction was after 2 hours 24% (from 73.1 mm to 55.5 mm) in the active group and 13% (from 73.6 mm to 63.9 mm) in the placebo group; after 48 hours these percentages were 45% (28.5 mm) and 30%, (44.1mm) respectively. These data were further supported by secondary outcome measures such as the percentage of patients with meaningful pain relief defined as 50% reduction in pain score. The proportion of subjects with meaningful pain relief at 2 hours was 38% and 12% for lidocain and placebo respectively. Onset of meaningful pain relief was 0.4 hours for the lidocaine and 0.7 hours for placebo. This study confirmed the results of the previously submitted placebo controlled study.

No clinically relevant differences in adverse effects were observed between lidocaine lozenges and placebo. Lidocaine lozenges were well tolerated.

It is concluded that on basis of the results of the two placebo-controlled studies, Lidocaine 8 mg lozenges used in the treatment pharyngeal pain due to acute non-bacterial pharyngitis is efficacious and safe.

Literature overview

In a literature overview of the clinical experience on lidocaine as a local anaesthetic used in the mouth, nose, trachea-bronchial tree, oesophagus, and genitourinary tract was shown that Lidocaine is usually used at a concentration of 2% and that topical application can provide clinically significant pain relief. Its use for the relief of pain of sore throat is an extension of its use in topical anaesthesia. An overview of safety data demonstrated that adverse effects of lidocaine can only be expected at high plasma concentrations of the drug, and are not to be expected with the recommended dosage of lidocaine 8 mg lozenges.

Risk Management Plan

Lidocaine was first approved in 1974 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lidocaine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

During the assessment it was noted that local anaesthetic effects may interfere with swallowing and enhance the danger of aspiration (risk of choking) when (more) frequently dosed. This can be particularly dangerous in children because of their frequency of eating (presently not tested). Numbness of the tongue or buccal mucosa may increase the danger of biting trauma. Therefore, a warning was included in the SPC stating that ingestion of food and drinks immediately after use of the lozenges should be avoided. Furthermore, a contra-indication for children younger than 12 years was added.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 6 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III CONCLUSION AND BENEFIT-RISK ASSESSMENT

Trachisan 8 mg, lozenges have a proven established chemical-pharmaceutical quality.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

In a dose finding study a dose relationship was observed for, 2, 4, or 8 mg lidocaine lozenges. In two placebo-controlled studies Lidocaine 8 mg lozenges used in the treatment of pharyngeal pain due to acute non-bacterial pharyngitis showed efficacy compared to placebo and was as safe and well tolerated .

Two placebo-controlled studies demonstrated that Lidocaine 8 mg lozenges, used in the treatment pharyngeal pain as a symptom of acute non-bacterial pharyngitis, have a statistically significant efficacy compared to placebo and were safe and well tolerated.

The efficacy and safety of lidocaine as a local anaesthetic used in the mouth, nose, trachea-bronchial tree, oesophagus, and genitourinary tract was further confirmed in a literature overview. The dose recommendations included in the SPC are justified by pharmacokinetic and clinical data.

During the procedure, a warning was included in the SPC stating that ingestion of food and drinks immediately after use of the lozenges should be avoided. Furthermore, a contra-indication for children younger than 12 years was added. The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Trachisan 8 mg, lozenges was authorised in the Netherlands on 24 June 2004. The concerned member states, on the basis of the data submitted, considered that Trachisan had a positive benefit/risk profile for the indication *"Short-term local treatment of pain associated with sore throat in non-purulent infections"*, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 22 December 2006.

The PSUR has been submitted semi-annually. The first PSUR was submitted in December 2005, from then on semi-annually. The last PSUR was submitted in December 2008.

The date for the first renewal will be: 24 June 2009.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name of the medicinal product in Greece.	NL/H/0926/001/IB/001	IB	6-8-2008	5-9-2008	Approval	N
Change in the name of the medicinal product in Estonia.	NL/H/0926/001/IB/002	IB	23-10-2008	22-11-2008	Approval	N
Change in the name of the medicinal product in Latvia.	NL/H/0926/001/IB/003	IB	5-1-2009	5-2-2009	Approval	N
Renewal of the marketing authorisation.	NL/H/0926/001/R/001	Renewal	17-4-2009	13-2-2010	Approval	Y, Annex I
1)Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. Re-test period/storage period reduction. 2)Submission of a new or updated Ph. Eur. certificate of suitability: ror an excipient. European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. Updated certificate from an already approved manufacturer.	NL/H/0926/001/IA/004/G	IA/G	22-6-2010	22-7-2010	Approval	N
Change in the specification parameters and/or limits of the finished product. Addition of a new specification parameter to the specification with its corresponding test method.	NL/H/0926/001/IA/005	IA	22-6-2010	22-7-2010	Approval	N
Changes in the composition (excipients) of the finished product; changes in components of the flavouring or colouring system.	NL/H/0926/001/IA/006	IA	14-7-2010	13-8-2010	Approval	N
Change in the specification parameters and/or limits of the finished product. Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter).	NL/H/0926/001/IA/007	IA	14-7-2010	13-8-2010	Approval	N

Annex I – Renewal of the marketing authorisation

I Introduction

Trachisan Lozenges (NL/H/926/01/R/01) contain lidocaine hydrochloride as active ingredient. The product Trachisan (NL/H/926/01/R01) is indicated for short-term local treatment of pain associated with sore throat in non-purulent infections. These lidocaine lozenges were authorised through Mutual Recognition Procedure with Netherlands as RMS.

The MAH submitted a response, dated 13 July 2009, to the RMS' comments upon the documents submitted in scope of the first Renewal of the products. This response also encompassed revised versions of the SPCs.
The MAH comments were in general that as agreed with the RMS the next PSUR should be submitted with DLP December 2009 based upon the EU HBD. The next PSUR should hereafter be submitted after three years with DLP December 2012.

II Assessment of the responses to the Member State(s) Request for supplementary information

II.1 Questions on PSURs

Comment:

1. Besides monitoring the issue, the MAH should consider including methaemoglobinaemia in the SPC.

Response MAH:

The MAH has additionally performed a Medline search to obtain more information on the potential risk of methaemoglobinaemia in association to lozenge administration. After the analysis of all results the MAH is aware of the occurrence of methaemoglobinaemia in relation to the administration of local anaesthetics, especially benzocaine and prilocaine.
However, in the majority of reports on this side effect, the anaesthetic drugs have been administered through a route of administration different from lozenges, or lidocaine has been administered in combination with prilocaine/benzocaine topically in neonates or preterm infants and the methaemoglobin levels remained normal or below potentially harmful levels without signs of toxicity. According to the SPC, lidocaine lozenges are contraindicated in patients younger than 12 years so that a risk in this target population is minimized.
Lidocaine lozenges have a low absorption rate and reduced bioavailability so that systemic adverse reactions are highly improbable (undesired systemic effects only occur when blood plasma levels reach levels above 5- 10 µg lidocaine per ml).

No case from any source on the occurrence of methaemoglobinaemia in relation to lozenges has been received by the MAH.

The current status of information does not suggest a potential risk for the occurrence of this side effect after use of lidocaine in form of lozenge formulations, which would require amendments of the SPC.
However, the MAH cconsiders that methaemoglobinaemia in relation to the administration of lidocaine lozenges is a safety issue that requires close monitoring and it is committed to re-evaluate this topic on a regular basis and to re-consider based on the cumulative experience if the term should be included in the undesirable effects section of the SPC.

Response assessment: The response of the MAH is acceptable. The conclusion not to include methaemoglobinaemia as adverse reaction in the SPC, but to continue close monitoring the issue is currently agreed upon. Issue resolved.

Comment:

2. As indicated in the Renewal Guideline the clinical expert in the clinical expert statement should also confirm that no new (pre-clinical or clinical) data are available which change or results in a new benefit-risk evaluation. (Where there are new pre-clinical data the MAH may submit a non-clinical expert report as appropriate). Please adapt the Clinical Expert Statement as appropriate.

Response MAH:

The MAH agrees and has updated the clinical expert statement.

Response assessment: The clinical expert statement has been amended to include that no new (pre-)clinical data are available which changes or results in a new benefit-risk evaluation. Issue resolved.

Comment:

3. The company mentions that in order to take account of technical and scientific processes several changes are introduced to module 3. However, module 3 should not be updated at the time of the renewal. The MAH should clarify if module 3 requires to be updated. Any proposed changes should be submitted via a separate type II variation.

Response MAH:
The applicant agrees and the proposed changes of Module 3 will besubmitted via a separate type II variation at the end of the renewal procedure.

Comment:

4. The MAH should closely monitor the interaction of the products with CYP1A2 and CYP3A4 inhibitors.

Response MAH:

The MAH agrees and has initiated monitoring for potential interactions of lidocaine lozenges with CYP1A2 and CYP3A4 inhibitors.

Comment:

5. The MAH should be aware of special patient groups, such as children and elderly.

Response MAH:

MAH agrees. Safety issues in special patient groups will be specially taken into consideration and they will be specifically reflected in the corresponding PSUR section in the future.

Comment:

6. Preferably all literature cases relating to topical use of lidocaine should be included in the PSUR since the issues identified may also be of relevance to the products of the current MAHs.

Response MAH:

The MAH agrees with the assessor's comment and commits to evaluate literature case reports in future PSURs, in which lidocaine has been administered topically. Cases of mucosal exposure will be especially taken into account. Furthermore, for safety reasons cases in which cutaneous or transdermal administration of lidocaine has been associated to systemic adverse reactions will also be included.

Comment RMS:

7. In future submissions one PSUR should be submitted covering all lidocaine lozenges MAs with all information combined in this single document.

Response MAH:

The MAH has responded that the MAH's for Nolaid NL/H/494/01 and Trachisan NL/H/926/01 will not be working together in these dossiers and will therefore submit separate PSURs.

II.2 Questions on SPC/ Package Leaflet/ Labelling

SPC

Comment:

1. The SPCs for Nolaid and Trachisan differ with some respects. Please fully harmonise the information in these SPCs as well as adapt to the latest QRD template.

   Section 4.8 of the SPCs needs to be updated to the current Guideline on SPC, dated October 2005. The new frequency convention should be used and the frequencies should not be explained in the 'table' of adverse reactions.

Response MAH:

The respective SPC/PL and Label have been revised and adapted to the latest QRD template as requested by the RMS.

Furthermore, as requested by the RMS harmonisation of both texts has been carried out. However, most of the amendments regarding harmonisation of both texts have been made to the Nolaid text since the Trachisan text complied more closely with the current QRD template.

Section 4.8 has also been amended. The frequencies have been corrected to the most current ones (QRD appendix II, version 02_2009, MedDRA version 12.0). As requested by the RMS the frequencies have been deleted from the AE table. The SOCs are already given in the most current order and do not need further amendment.

Response assessment: The MAH has proposed several revisions in the currently approved SPC. Please see section IV for an overview of all changes.

The MAH has harmonised the product information from Trachisan (NL/H/926) and Nolaid (NL/H/494) which is considered acceptable.

Furthermore, the MAH has reworded some parts of section 4.2; 4.3 and 4.4 or moved some of the information within each section. These rewordings however do not change the content/ advice in these sections and are therefore considered acceptable.

The changes with respect to section 4.8 of the SPC are agreed upon.

With respect to section 4.6 the MAH has now proposed a revised wording for the section pregnancy:

Controlled clinical trials in pregnant women are not available. ~~Limited d~~**D**ata on **a limited number of** exposed pregnancies ~~showed~~ **indicate** no **adverse effects of lidocaine on pregnancy or on the health of the foetus/new new-born child** ~~evidence on congenital anomalies~~. Lidocaine passes the placenta after parenteral use.

Although harmonisation was requested of the product information of Nolaid (NL/H/494) and Trachisan (NL/H/926), now a new proposal is submitted only for Trachisan NL/H/926 without further substantiation. Since the current information suffices the original text should be maintained.

Comment :

2. In the presented SPC the finished product storage conditions have been stated "*Do not store above 25C. Do not refrigerate or freeze. Store in the original package*". According to the "*Note for guidance on declaration of storage conditions: A: In the product information of medicinal products B: For active substances*" it should be specified if the product is sensitive to light and/or moisture.

Response MAH

The applicant agrees to the comment. The respective storage recommendation has been amended considering also the comment of the RMS to adapt the text to the current QRD template.

Response assessmentt: The MAH has made the following amendment:

Store in the original package **in order to protect from moisture**

The active substance lidocaine HCl is not sensitive to light or humidity. However, considering that the tablet base is 684.50 mg of sorbitol which is a hygroscopic powder and the performance of the dosage form might be affected by the increase of water content and loss of hardness, it is required to store the product in the original product in order to protect from moisture.

Therefore the proposed change to section 6.4 of the SPC is considered acceptable.

Package leafet

Comment:

3. The package leaflet and labelling for Nolaid and Trachisan should be revised, if applicable, due to the above mentioned comments on the SPC.

Response MAH

The respective SmPC/PL and Label have been revised and adapted to the latest QRD template as requested by the RMS. Changes to the SmPC relevant to the label text have been transferred accordingly. Furthermore, as requested by the RMS harmonisation of both texts has
been carried out. However, most of the amendments regarding harmonisation of both texts have been made to the Nolaid text since the Trachisan text complied more closely with the current QRD template.

Response assessment: The MAH has proposed several revisions in the currently approved Package leaflet. Please see section IV for revisions.

2. Before you take Trachisan 8 mg lozenges
*The MAH has relocated some of the information in this section (e.g. warnings concerning risk for impaired swallowing and risk of aspiration is now mentioned in the section '*Taking Trachisan 8 mg Lozenges with food and drink'*) which is considered acceptable.*

Furthermore the MAH has made the following change in this section:

~~Children and a~~Adolescents **(12 to 17 years)**

~~Children under 12 years of age must not take Trachisan 8 mg (see above~~).

There is not sufficient information on the use of Trachisan **8 mg** **I**~~L~~ozenges in ~~children and~~ adolescents 12 to 17 years of age with respect to efficacy and tolerability. Therefore, the use of Trachisan 8 mg **I**~~L~~ozenges is not recommended in ~~children and~~ adolescents 12 to 17 years of age.

Although it is correct that in the section 'Do not take…' it is already mentioned that children under 12 years of age must not take Trachisan, it is not agreed to delete the information concerning children under 12 years of age in this section. If a patient requires information in the package leaflet concerning children and adolescents, a section concerning only adolescents may be confusing. Therefore, the original text should be maintained also given the importance of the content.

Furthermore, some revisions are proposed by the RMS to harmonise the package leaflet with other lidocaine-containing lozenges (Nolaid NL/H/494). Please see section IV.

Comment:

4. In the presented Package leaflet the finished product storage conditions have been stated "*Do not store above 25ºC. Do not refrigerate or freeze. Store in the original package*". According to the "*Note for guidance on declaration of storage conditions: A: In the product information of medicinal products B: For active substances*" it should be specified if the product is sensitive to light and/or moisture.

Response MAH

The applicant agrees to the comment of EE to the SmPC. Since the storage recommendation has been amended in the SmPC and this amendment is relevant for the PL, the respective amendment has additionally been made to the PL text.

Comment:

5. In section "*Taking other medicines*" all medicines which may react with lidocaine should be listed with patient friendly explanation when these medicines are used.

Response MAH

The applicant disagrees. First it has to be emphasised that all these interactions are not of clinical relevance when lidocaine is applied in form of lozenges (this is already stated in the SmPC) and are hence not relevant for the patient (but quite the contrary can be misleading). Second this PL has been user tested and no request to include all interactions has been raised thereby.

Response assessment. The RMS agrees with the MAH. All interactions mentioned in section 4.5 of the SPC are not considered clinically relevant and therefore it is not useful to include such information in the package leaflet.

Comment:

6. In section "*If you take more Trachisan 8 mg than you should*" vomiting should be added.

Response MAH

The applicant agrees. The current PL text of the respective section now reads: "*If you take a very high number of Trachisan 8 mg overdosage of lidocaine may occur and cause symptoms such as yawning, restlessness, dizziness, feeling or being sick, dysarthria (speech disorder due to some disorder in the nervous system), hearing and visual disturbances as well as disorders of coordination of movements."*

.
The term "*being sick*" has been used as the patient-friendly wording for "*vomiting*".'

Labelling

Comment RMS

7. The package leaflet and labelling for Nolaid and Trachisan should be revised, if applicable, due to the above mentioned comments on the SPC.

Response MAH
The respective SmPC/PL and Label have been revised and adapted to the latest QRD template as requested by the RMS. Changes to the SmPC relevant to the label text have been transferred accordingly.

Furthermore, as requested by the RMS harmonisation of both texts has been carried out. However, most of the amendments regarding harmonisation of both texts have been made to the Nolaid text since the Trachisan text complied more closely with the current QRD template.

However, due to reasons of reiteration (and also due to problems of space) one reference to the PL has been deleted.

Response assessment: The proposed labelling is attached separately. No major changes are proposed. The reference to the package leaflet was included twice and therefore it is acceptable that one reference is deleted. The proposed labelling is considered acceptable.

Comment:

8. In the presented SPC the finished product storage conditions have been stated "*Do not store above 25ºC. Do not refrigerate or freeze. Store in the original package*". According to the "*Note for guidance on declaration of storage conditions: A: In the product information of medicinal products B: For active substances*" it should be specified if the product is sensitive to light and/or moisture.

Response MAH

The applicant agrees with the comment to the SmPC. Since the storage recommendation has been amended in the SmPC and this amendment is relevant for the label, the respective amendment has additionally been made to the label text.

Comment:

9. According to the Annotated QRD Template, all excipients should be listed.

Response MAH
The applicant agrees. All excipients will be listed on the outer packaging as requested by the QRD template for topically used medicinal products.

III Conclusions

Assessment of the responses of the MAH to the RMS' comments on the documents submitted in scope of the Renewal of the products, led to the following conclusions:

- With respect to the SPC:
  - With respect to the section 4.6 of the SPC a new proposal is submitted for Trachisan NL/H/926 without further substantiation. Since the current information suffices, the original text should be maintained.

- With respect to the Package Leaflet:
  - the original text regarding children and adolescents should be maintained in the section "*2. Before you take Trachisan 8 mg lozenges*".
  - Furthermore, some revisions are proposed by the RMS to harmonise the package leaflet with other lidocaine-containing lozenges (Nolaid NL/H/494).

- With respect to the PSUR:
  - The next PSUR should be submitted with DLP December 2009 based upon the EU HBD.
  - Thereafter, the PSUR should hereafter be submitted after three years with DLP December 2012.

The MAH has adequately responded to the outstanding issues regarding the SPC and package leaflet. Therefore, renewal was granted with unlimited validity.

IV Revisions to SPC and Package Leaflet (PL)

Small revisions (typo's, etc.) are not metioned here.

IV.1 SPC revisions

Section 4.2 Posology and method of administration

Children:
~~Children younger than 12 years of age should not take this medicinal product (see section 4.3).~~ Trachisan 8 mg is contraindicated in children below 12 years (see section 4.3).

Adolescents:
~~There are insufficient efficacy and safety data to recommend the use of Trachisan 8 mg in children in the age of 12 - 17 years. (see section 4.4)~~ Trachisan 8 mg is not recommended for use in adolescents in the age of 12 - 17 years due to insufficient data on safety and efficacy (see section 4.4).

Section 4.3 Contraindications

~~Patients younger than 12 years should not take Trachisan 8 mg (see section 4.4).~~ Trachisan 8 mg is contraindicated in patients below 12 years (see section 4.4).

Section 4.4 Special warnings and precautions before use

~~Trachisan 8 mg contain sorbitol.~~

~~Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol can cause gastro-intestinal disorders and diarrhoea.~~

Lidocaine is predominantly metabolised in the liver, the metabolites are predominantly eliminated by the kidneys. In patients with reduced function of the liver and / or kidneys the plasma levels of lidocaine or its metabolites can be increased.

This effect will not be of clinical relevance when lidocaine is applied in form of a lozenge.
Local anaesthetics may interfere with swallowing and enhance the danger of aspiration, especially in young children because of their frequency of eating (see section 4.3). Ingestion of food and drinks immediately after use of the lozenges should be avoided. Numbness of the tongue or buccal mucosa may increase the danger of biting trauma. There is an increased risk of mouth and throat mucous burns with hot drinks and food due to decreased sensibility of warmth. Repeated use may lead to a numb throat, resulting in swallowing difficulties.

~~The use of Trachisan 8 mg in children in the age of 12 - 17 years can not be recommend since there are insufficient efficacy and safety data.~~ Trachisan 8 mg is not recommended for use in adolescents in the age of 12 - 17 years due to insufficient data on safety and efficacy.

Trachisan 8 mg should be used with caution in patients with severely traumatised and/or inflammation of oropharyngeal mucosa, in particular in patients with underlying cardiovascular or convulsive disorders.

A cross allergy to lidocaine hydrochloride must be expected in patients with a known history of allergy to other local anaesthetics of the amide type.

In order to avoid further complications, Trachisan 8 mg should not be taken for longer than two days without consulting a physician if severe throat inflammations or sore throats continue and are accompanied by fever, headaches, nausea or vomiting.

Trachisan 8 mg contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Section 4.6 Pregnancy and lactation

Pregnancy
Controlled clinical trials in pregnant women are not available. ~~Limited d~~Data on a limited number of exposed pregnancies ~~showed~~ indicate no adverse effects of lidocaine on pregnancy or on the health of the foetus/new-born child ~~evidence on congenital anomalies~~. Lidocaine passes the placenta after parenteral use.

Section 4.8 Undesirable effects

Very common:	≥~~>~~1/10
Common:	≥~~>~~1/100 ~~and~~ to <1/10
Uncommon:	≥~~>~~1/1,000 ~~and~~ to <1/100
Rare:	≥~~>~~1/10,000 ~~and~~ to <1/1,000
Very rare:	<1/10,000 ~~including isolated cases~~
Not known:	Frequency cannot be estimated from the available data

The possible side effects after using Trachisan 8 mg are similar in nature to those usually to be expected with other amide local anaesthetics. Undesired systemic effects only occur when blood plasma levels reach levels above 5-10 µg lidocaine per ml. Therefore, due to its low absorption rate, systemic adverse reactions when using Trachisan 8 mg are not to be expected.

Immune system disorders
Very rare ~~(<1/10 000)~~: hypersensitivity reactions or sensitisation in the oral region ~~may occur~~.

Gastrointestinal disorders
Rare ~~(>1/10 000 and <1/1000)~~: gustatory changes or numbness of the tongue. These effects usually disappear after a short time.
Very rare ~~(<1/10 000)~~: laxative effect due to the sorbitol contents.

Section 6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original package in order to protect from moisture.

IV.2 Package Leaflet revisions

Section 2 Before you take Trachisan 8 mg

Do not take Trachisan 8 mg
- if you are allergic (hypersensitive) to lidocaine hydrochloride or other amide-type local anaesthetics or any of the other ingredients of Trachisan 8 mg.
- children under 12 years of age must not take Trachisan 8 mg.

Take special care with Trachisan 8 mg

- if you have a severely inflamed or sore throat accompanied by a high temperature, headache, feeling sick or being sick. In these cases you must not take Trachisan 8 mg for more than 2 days without consulting a doctor in order to prevent complications.

- in patients with severe injuries and/or inflammations of the mucosa of the mouth and throat because the absorption (uptake) of the active substance may be increased. This applies in particular to patients with cardiovascular disorders or a susceptibility to convulsions.

- ~~Local anaesthetics may impair swallowing and increase the risk of aspiration, particularly in young children. Trachisan 8 mg should therefore not be used in children under 12 years of age (see above). You should not eat or drink immediately after you have taken the lozenges. Numbness of the tongue and oral mucosa can increase the risk of injuries due to biting. Be cautious with hot drinks and food. There is an increased risk of mouth and throat mucous burns due to decreased sensibility of warmth. Repeated use can cause numbness of the throat and hence to difficulties swallowing.~~

- in patients with impaired liver and/or kidney function because these conditions can cause elevated blood concentrations of the active substance.

- if you know that you are allergic to other local anaesthetics of the amide-type, since you may then also be allergic to lidocaine.

Children and adolescents ~~(12 to 17 years)~~
Children under 12 years of age must not take Trachisan 8 mg (see above).

There is not sufficient information on the use of Trachisan 8 mg in children and adolescents ~~12 to 17 years of age~~ with respect to efficacy and tolerability. Therefore, the use of Trachisan 8 mg is not recommended in ~~children and~~ adolescents 12 to 17 years of age.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Trachisan 8 mg with food and drink

Local anaesthetics may impair swallowing and increase the risk of aspiration, particularly in young children. You should not eat or drink immediately after you have taken Trachisan 8 mg in order to prevent aspiration or injuries due to biting ~~(see above)~~.

Be cautious with hot drinks and food. There is an increased risk of mouth and throat mucous burns due to decreased sensibility of warmth. Repeated use can cause numbness of the throat and hence to difficulties swallowing.

Pregnancy
You ~~must~~ should not take Trachisan 8 mg when you are pregnant unless considered clearly necessary by a doctor.

~~Ask your doctor or pharmacist for advice before taking any medicine.~~

Breast-feeding
~~Ask your doctor or pharmacist for advice before using Trachisan 8 mg.~~
Lidocaine enters the mother's milk in such small quantities that when using Trachisan 8 mg as instructed, a safety concern for the child of breast feeding women appears very unlikely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Trachisan 8 mg has no influence on the ability to drive and use machines.
~~When taken as directed an impairment of the ability to drive is not to be expected.~~

Important information about some of the ingredients of Trachisan 8 mg
Trachisan 8 mg contains sorbitol. ~~1 lozenge contains 0.68 g sorbitol.~~ If you have been told by your doctor that you have an intolerance to some sugars, ~~please~~ contact your doctor before using this medicinal product.

~~Sorbitol can cause gastrointestinal disorders and diarrhoea.~~

Section 3 How to take trachisan 8 mg

~~Unless otherwise directed by your doctor~~ The usual dose is:
Adults take 1 lozenge at intervals of at least 2 hours. Do not take more than 6 lozenges per day. Slowly dissolve Trachisan 8 mg in the mouth.

Section 4 Possible side effects

Like all medicines, Trachisan 8 mg can cause side effects, although not everybody gets them.

The assessment of side effects is based on the following frequencies:

Very common:	affects more than 1 user in 10 ~~patients treated~~
Common:	~~Less than 1 of 10, but more than 1 of 100 patients treated~~ affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000 ~~Less than 1 of 100, but more than 1 of 1000~~
Rare:	affects 1 to 10 users in 10,000 ~~Less than 1 of 1000, but more than 1 of 10,000 patients treated~~
Very rare:	affects less than 1 user in 10,000 ~~Less than 1 of 10,000, including isolated reports~~
Not known	frequency cannot be estimated from the available data

~~Immune system disorders~~
~~Very rare: Hypersensitivity reactions or sensitisation in the mouth can occur.~~

~~Gastrointestinal disorders~~
Rare:
- Due to the desired analgesic effect the sense of taste may be affected or numbness of the tongue may occur. These effects usually disappear after a short period of time.

Very rare:
- Hypersensitivity reactions or sensitisation in the mouth can occur.
- Sorbitol contained in this product can have a laxative effect.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Section 5 How to store Trachisan 8 mg

Keep out of the reach and sight of children.

Do not use Trachisan 8 mg after the expiry date which is stated on the blister pack and the outer carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Section 6 Further Information

What Trachisan 8 mg contains
- The active substance is lidocaine hydrochloride. Each lozenge contains 8 mg lidocaine hydrochloride (as monohydrate).
- The other ingredients are: sorbitol, peppermint oil, magnesium stearate .

What Trachisan 8 mg looks like and contents of the pack

Trachisan 8 mg lozenges are white and round flat lozenges with bevelled edge.

Trachisan 8 mg is available in packs of 2, 10, 12, 16, 20, 24, 30, 36, 40, 48, 50, 60 and 100 lozenges.

Not all pack sizes may be marketed.