CBG MEB

Public Assessment Report

Scientific discussion

Maeliloz Mint, Orange and Honey & Lemon lozenges

(2, 4-dichlorobenzyl alcohol/amylmetacresol/lidocaine)

NL/H/2988/001-003/DC

Date: 13 April 2016

This module reflects the scientific discussion for the approval of Maeliloz Mint, Orange and Honey & Lemon lozenges. The procedure was finalised on 11 February 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Maeliloz Mint, Orange and Honey & Lemon lozenges from MAE Holding BV.

The product is indicated for relief of symptoms of sore throat in adults and adolescents over 12 years of age.

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

This decentralised procedure concerns a hybrid application with reference to Strepsils Lidocaine pastilles which have been registered in Belgium by Reckitt Benckiser Healthcare NV/SA since November 1999.

The concerned member states (CMS) involved in this procedure were Belgium (only mint and honey & lemon), Czech Republic, Denmark, Germany, Norway, Poland, Slovakia and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, given the product is locally applied and locally acting.

The lozenges contain three well-known active substances: lidocaine, amylmetacresol and 2, 4-dichlorobenzyl alcohol. In the Netherlands, amylmetacresol and 2, 4-dichlorobenzyl alcohol are antiseptics present in the registered Strepsils lozenges: Original (NL License RVG 04174), Lemon & Honey (RVG 06556), Orange & Vitamin C (RVG 10987) and Cool (RVG 14597). All these products have the same indication, posology and route of administration, but they do not contain lidocaine. The aim of adding lidocaine to the formulation is to exercise an analgesic-local anaesthetic action in the oral cavity and pharynx region that enhances the antiseptic (and slight local anaesthetic) effect of amylmetacresol and 2, 4-dichlorobenzyl alcohol.
Lidocaine is a well-known local anaesthetic. For treatment of a sore throat, it is approved in the Netherlands in Trachitol lozenges (NL License RVG 03432). Moreover, reference can be made to Strepsils Lidocaine lozenges registered elsewhere in Europe.

II. QUALITY ASPECTS

II.1 Introduction

Maeliloz Mint are green, biconvex, cylindrical, mint-flavoured lozenges.
Maeliloz Orange are orange, biconvex, cylindrical, orange-flavoured lozenges.
Maeliloz Honey & Lemon are yellow, biconvex, cylindrical, honey and lemon-flavoured lozenges.

Each lozenge contains:

Lidocaine Hydrochloride	2.00 mg
Amylmetacresol	0.60 mg
2, 4-Dichlorobenzyl Alcohol	1.20 mg

The lozenges are packed in PVC-PVDC/Aluminium blisters.

The excipients are:
Maeliloz Mint - mint oil, partly dementholised, star anise oil, levomenthol, indigo carmine (E-132), quinoline yellow (E-104), sodium saccharin (E-954), tartaric acid (E-334), sucrose, liquid glucose.
Maeliloz Orange - levomenthol, sodium saccharin (E-954), sucrose, liquid glucose, sunset yellow (E-110), cochineal red (E-124), citric acid monohydrate (E-330), orange flavour.
Maeliloz Honey & Lemon - mint oil, partly dementholised, quinoline yellow (E-104), sodium saccharin (E-954), tartaric acid (E-334), sucrose, liquid glucose, sunset yellow (E-110), lemon essence, honey flavour.

II.2 Drug Substances

2,4-dichlorobenzyl alcohol
The active substance 2,4-dichlorobenzyl alcohol is an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). The active substance is very slightly soluble in water. The molecule has no chiral centre.

The Active Substance Master File (ASMF) procedure is used for 2,4-dichlorobenzyl alcohol. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis comprises two reaction steps. The product is then dried and sieved. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 30°C/60% RH (36 months) and 40°C/75% RH (6 months). The proposed re-test of 3 years without special storage conditions is accepted based on the results.

Amylmetacresol
Amylmetacresol is an established active substance described in the European Pharmacopoeia.

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 suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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., and an additional tests included on the CEP for a residual solvent.

Stability of drug substance
The active substance amylmetacresol is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Lidocaine HCl
Lidocaine HCl is an established active substance described in the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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., and an additional tests included on the CEP for a residual solvent.

Stability of drug substance
The active substance lidocaine is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the drug product has been described, the choice of excipients is justified and their functions explained. The aim of the development of the drug product was to mimic the innovator product. A dosage form of this drug product was first characterised. The colour and taste was mimicked. The impurity profile was compared with the innovator. Comparative dissolution profiles at pH 6.2 demonstrated similarity to the innovator product. For lozenges, there is no specific guidance. They concern a locally acting medicine with systemic activity when swallowed accidentally. If swallowed, the drug substances will be absorbed in the duodenum, which has a similar pH as the oropharyngeal cavity. Hence, it is unlikely that this will have safety repercussions. A study investigating buccal release was submitted in the clinical part of the dossier, as discussed in section IV of this report.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has sufficiently been described and consists of blending, colouring, kneading, rolling, cooling, sorting and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches per flavour. The product is manufactured using conventional manufacturing techniques.

Control of excipients
Several of the excipients in the final product composition are not described in any pharmacopoeia: Indigo carmine colouring, Quinoline yellow, Yellow-orange colouring, Cochineal red colouring, Orange flavour, Lemon essence and Honey flavour. Specifications and certificates of analysis of all these substances have been provided. The analytical procedures and validation of the analytical procedures used for the non-compendial methods have been described. The other excipients comply with the Ph.Eur. and are therefore acceptable.

Quality control of drug product
The product specification includes tests for appearance, mean weight, uniformity of dose, assay, ethanol, loss on drying, related substances and microbiological control. The release and shelf-life limits are identical with the exception of ethanol content and loss on drying. The analytical methods have been adequately described.
Batch analytical data from the proposed production site have been provided on three full-scale batches per flavour, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three batches per flavour stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The product was shown to be photostable. Based on the stability results a shelf life of 27 months packed in the PVC/PVDC-Al blister with a storage condition of ‘do not store is 30°C’ was proposed and found acceptable.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Maeliloz Mint, Orange and Honey & Lemon lozenges have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name): lidocaine			
CAS-number (if available): 137-58-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake flask method	2.76 at pH ~10; 23°C	not B
	HPLC method	3.4 at pH 11.2; 21°C	Not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.76 - 3.4	Not B
PBT-statement:	not yet concluded		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen} F_{pen} refinement not yet accepted	0.080	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	not investigated		

Conclusions on lidocaine

The $PEC_{surfacewater}$ for lidocaine is above the action limit of 0.01 µg/L. A refinement of F_{pen} or a Phase II assessment is deemed necessary. Lidocaine is not PBT, nor vPvB.

Substance (INN/Invented Name): amylmetacresol			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Applicant committed to perform an OECD 123	Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	study requested	PM
PBT-statement:	not yet concluded		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen} F_{pen} refinement not yet accepted	0.024	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	not investigated		

Conclusions on amylmetacresol

The $PEC_{surface\ water}$ for amylmetacresol is above the action limit of 0.01 µg/L. A refinement of F_{pen} or a Phase II assessment is deemed necessary.
The PBT assessment is pending, since data for log K_{ow} have not been agreed upon.

Substance (INN/Invented Name): 2,4-dichlorobenzyl alcohol			
CAS-number (if available): PM (identity requested, applicant gave incorrect CAS nr)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	study requested	Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	study requested	PM
PBT-statement:	not yet concluded		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen} F_{pen} refinement not yet accepted	0.048	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	not investigated		

Conclusions on 2,4-dichlorobenzyl alcohol
The $PEC_{surfacewater}$ for 2,4-dichlorobenzyl alcohol is above the action limit of 0.01 µg/L. A refinement of F_{pen} or a Phase II assessment is deemed necessary. Additional information regarding the ERA will be provided by the MAH post-approval.

III.2 Discussion on the non-clinical aspects

For this application reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

2, 4-dichlorobenzyl alcohol, amylmetacresol and lidocaine are well-known active substances with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted an *in vivo* study in which the amount of drug release from the proposed formulation was compared to the reference product, which is discussed below.

IV.2 Pharmacokinetics

A relative bioavailability study between the test formulation Maeliloz Mint lozenges (MAE Holding BV, the Netherlands) and the reference formulation Strepsils Lidocaine lozenges (Reckitt Benckiser Healthcare, France) has been submitted.

The composition of the Orange and Honey & Lemon lozenges differs only in the flavour making ingredients. These are considered not to affect the bioavailability of the active substances of the lozenges.

The choice of the reference product in the study has been justified. The formula and preparation of the batch used in the study is identical to the formula proposed for marketing.

Buccal release study

Design

The submitted study was a cross-over, two sequence, two period, randomised study in 44 healthy volunteers (27 females, 17 males), aged 18-55 years. Each subject received in a random way, seven oral doses of either test or reference formulation administered in two consecutive days (4 doses in Day 1 and 3 doses in Day 2, for each time point) per period, according to a two-period cross-over design. Prior to dosing each volunteer rinsed his mouth with 20 ml of still bottled water at room temperature that he was requested to afterwards drink.

The administration was performed in sitting position. The study medication was placed in the mouth, on the centre of the tongue and against the palate, and the subjects were requested to keep their mouths closed with the lozenge in the same position, except for the turning over of it at 360º every 30 seconds, on top of the tongue for 1, 2, 4, 6, 8, 10 or 12 minutes (according to the treatment duration foreseen in randomization table for the respective subject and administration). Subjects were asked to swallow the saliva generated, passing it through the lozenge at regular intervals, trying to move the lozenge as little as possible. The lozenges were not to be broken, chewed or swallowed nor moved, except for the turning over of it every 30 seconds. The time between two treatments on each day was 3 hours.

After consumption of the lozenges by the volunteers for the given time period, either 1, 2, 4, 6, 8, 10 or 12 minutes, the remaining unconsumed portions were diluted to obtain a matrix in which to measure the amounts of lidocaine, amylmetacresol and dichlorobenzyl alcohol. The consumption rates of the drug substances at each time for each lozenge were calculated based on the quantities of each drug substance in this remaining portion and on the amounts of each active substance present in 12 different lozenges of each of the formulations from the same batches, which were taken as baseline values.

This design was proposed given that the amount of each drug substance administered made it practically impossible to quantify them in blood. Moreover, given the characteristics of the product and the site of action, which is local in the area of administration, it appears that quantifying the amount released over time may be the best indicator of the behaviour of each one of the formulations. The bioavailability analysis in saliva was discarded due to the characteristics of this secretion, which varies greatly in both flow and composition. Under normal conditions, average saliva flow is 0.3 mL/minute, which may be stimulated by many circumstances, and with taste stimuli can reach 7 mL/minute under maximum stimulation. In addition, the fact that the flow is continuous and not constant, and that saliva is swallowed reflexively, it is impossible to collect all of the volume produced, and therefore to know exactly how much product has been released in this manner.

As the active substances are considered to act locally, measuring of systemic exposure will not contribute to the assessment of the efficacy of the product. The best way to measure the release from the lozenges would be measuring the concentration in salvia, however, it is agreed that the variability in production may be to high for a reliable estimate of the release from the lozenges.

Therefore the approach of MAH to measure the non-released amounts on several time points is considered acceptable.

Analytical/statistical methods

The analytical method used for determination of the three active ingredients in the medicinal products used are considered acceptable. The methods used for statistical evaluation are appropriate as well.

Results

Forty-two subjects completed the study and were included in the analysis, as two subjects withdrew of personal reasons.

The figures below show the mean dissolution profiles for the three active ingredients.

Figure 1: Mean values for the dissolution profiles for lidocaine

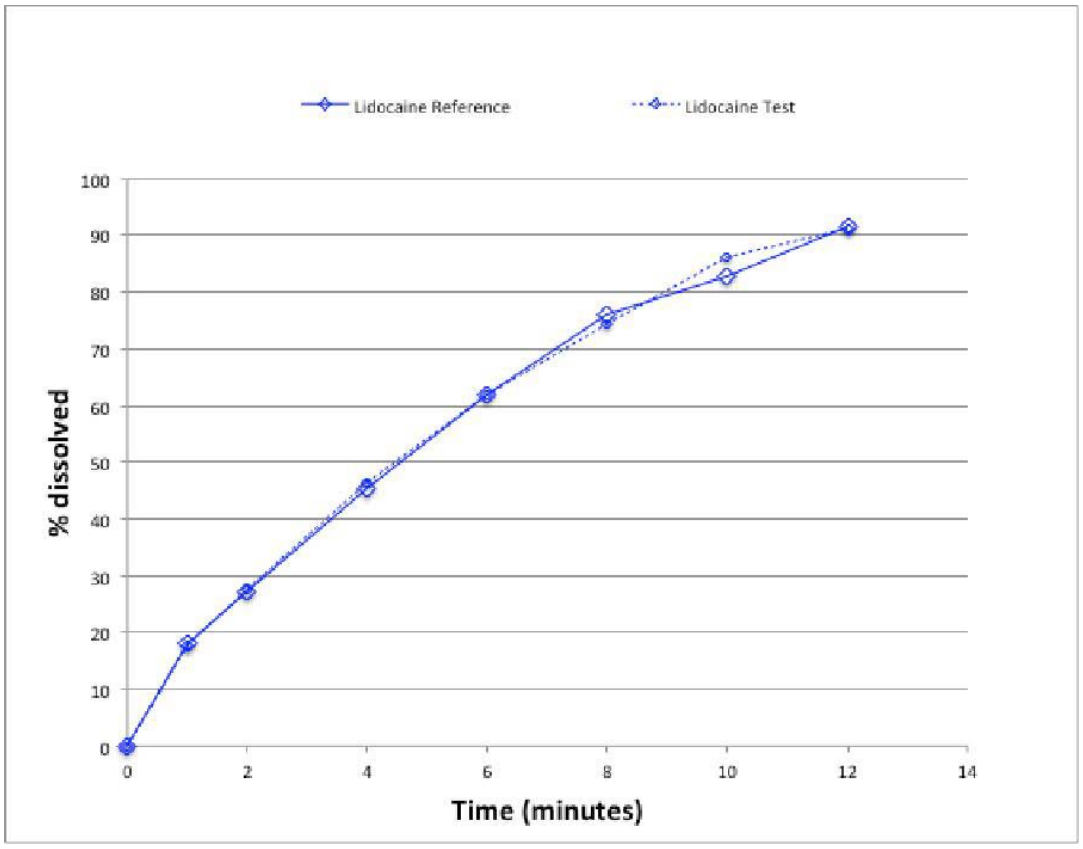


Figure 2: Mean values for the dissolution profiles for Amylmetacresol

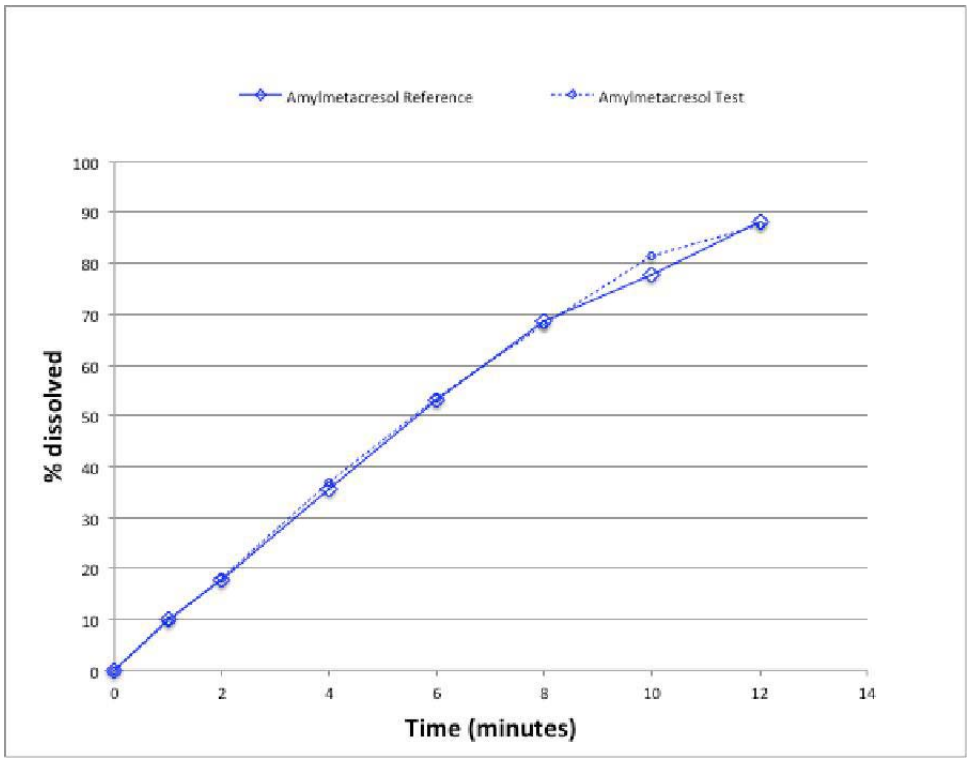
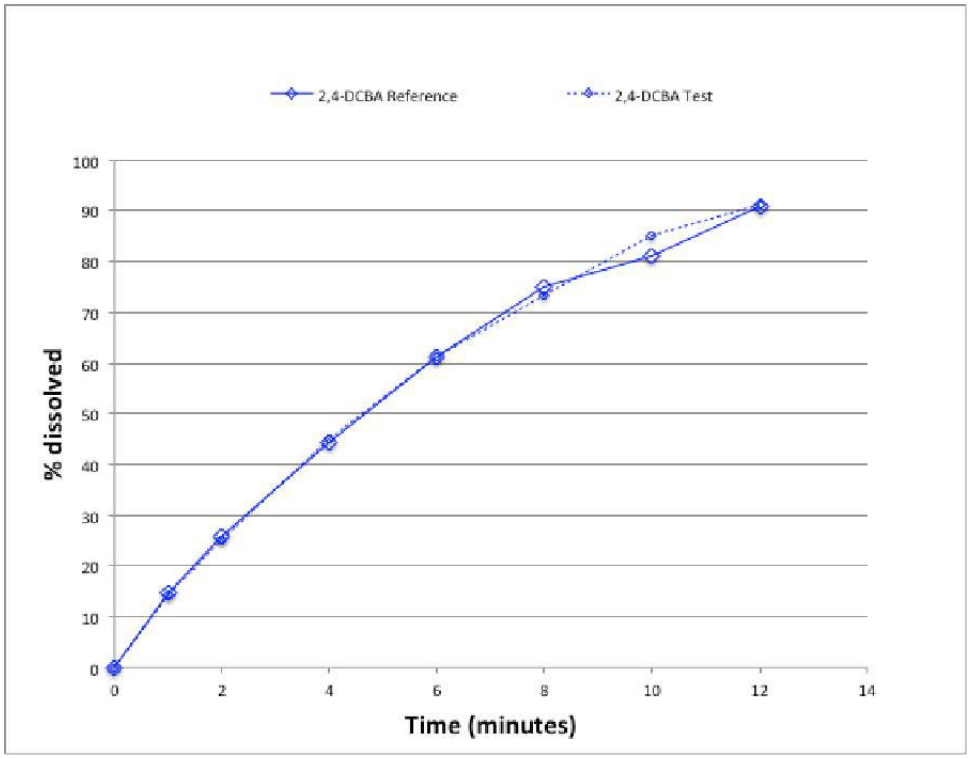


Figure 3: Mean values for the dissolution profiles for 2,4-DCBA



The similarity assessment was based on the calculation of the parameter f2 (similarity factor). As provided for in the bioequivalence guidelines ("Guideline on the investigation of bioequivalence" CPMP/QWP/EWP/1401/98 Rev 1), f2 values within the range of 50-100 may be considered similar for the comparison of dissolution profiles.
Calculation of f2 values were ≥ 85 for all three analytes, suggesting that the two formulations have very similar dissolution profiles, however the applicability of f2 was compromised due to high coefficient of variation (CV) registered (superior to 50% in all cases). Therefore, this analysis was presented only for traceability purposes.

Analyte	f2
Lidocaine	85.6
Amylmetacresol	86.1
2,4-DCBA	87.7

According to the protocol, Mahalanobis distance approach became primary efficacy parameter since applicability of f2 was compromised due to high CV registered. As shown in the following table, the similarity was established at 20% for all cases.

Analyte	Mahalanobis distance: Estimate[90%CI]	Conclusion
Lidocaine	0.51 [0.29 to 1.32]	U90%CI (1.32) is < Critical value of 10% (1.75)
Amylmetacresol	0.45 [0.35 to 1.25]	U90%CI (1.25) is < Critical value of 10% (1.57)
2-4-DCBA	0.65 [0.15 to 1.46]	U90%CI (1.46) is < Critical value of 10% (1.86)

The results of the Mahalanobis distance approach indicate that the upper bounds of the 90% confidence limits were inferior to the predefined critical value of the 20% distance between formulations, and to note, even below the critical value of the 10% distance between both formulations for all the active substances, thus allowing to conclude that the two study formulations are similar with respect to availability from the dosage form.

Study conclusion
A high variability in release has been observed which might have an impact on efficacy. The standard deviation and CV is large but of similar magnitude for both test and reference product. This implies that the distribution curves overlap. Based on the comparable variability, its unlikely that the clinical efficacy of test and reference product will be different. It should be noted though that the method used to shown equivalence is unusual and its acceptability remains uncertain. However, it is accepted that the test and reference products have comparative pharmaceutical quality and *in-vitro* dissolution profiles.
Overall, the results of the provided study with Maeliloz Mint lozenges show that the *in vivo* release of the three active substances can be considered similar with the reference product Strepsils Lidocaine lozenges.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Maeliloz lozenges.

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity (e.g. rash, urticaria, pruritus, mouth or pharyngeal oedema)	SmPC sections 4.3 and 4.8	None proposed
Pulmonary aspiration	SmPC section 4.4	None proposed
Impact on nervous system: convulsions, cardiac effects (when taken in large amounts or repeatedly)	SmPC section 4.4	None proposed
Important potential risks		
None		
Missing information		
Use in paediatric patients < 12 years	SmPC sections 4.3 and 4.4:	None proposed
Use in pregnancy and lactation	SmPC sections 4.6 and 5.3	None proposed

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies of, and experience with the reference product Strepsils Lidocaine lozenges. No new clinical studies were conducted. The MAH has demonstrated *in vivo* similarity to the reference product when it comes to release of the three active substances from the lozenges. Risk management is adequately addressed.

The SmPC is adequate for the use of this product in an OTC setting. A potential risk is that patients may not be aware that they have a serious angina where antibiotics may be required. Patients are therefore warned in the package leaflet to consult a physician if symptoms persist for longer than 2 days, get worse or if other symptoms appear, such as high fever, headache, nausea or vomiting, and skin rash. In the SmPC a recommendation has been included that in these cases, the clinical condition should be evaluated for bacterial infections (angina, tonsillitis).
The product is indicated for both adolescents and adults. There are no specific safety issues that would prevent the use of these lozenges in adolescents. Its use in this patient group is in accordance with the relevant EMA guidelines. Adolescents, under guidance of their care-takers, are in general considered capable to understand that the tablets should not be chewed or swallowed.
This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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, followed by two rounds with 10 participants each.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Maeliloz Mint, Orange and Honey & Lemon lozenges have a proven chemical-pharmaceutical quality and are hybrid forms of Strepsils Lidocaine lozenges. Strepsils is a well-known medicinal product with an established favourable efficacy and safety profile

Comparable buccal release of the active substances was shown in a study where the non-released amounts were assessed on several time points. This approach was sufficiently justified for this locally acting medicinal product.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Maeliloz Mint, Orange and Honey & Lemon lozenges with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 February 2015.

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
Inclusion of the following sentence in the posology of the PL: "maximum of 4 lozenges for children".	NL/H/2988/ 001-003/P/ 001	Art. 61(3)	22-6-2015	13-7-2015	Approval	No
Replacement or addition of a manufacturer responsible for importation and/or batch release: 1. Not including batch control/testing 2. including batch control/testing.	NL/H/2988/ 001-003/IA/ 002/G	IA/G	20-10-2015	19-11-2015	Approval	No
Change in product name in PL. Introduction of Pharmacovigilance System Master File.	NL/H/2988/ 001-003/IB/ 003/G	IB/G	21-12-2015	20-1-2016	Approval	No
Addition of a pack size for the medicinal product.	NL/H/2988/ 001-003/IB/ 004	IB	5-2-2016	6-3-2016	Approval	No