CBG MEB

Public Assessment Report

Scientific discussion

Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges

(amylmetacresol/2, 4-dichlorobenzyl alcohol)

NL/H/3307/001/DC

Date: 13 December 2016

This module reflects the scientific discussion for the approval of Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges. The procedure was finalised on 3 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADI	Acceptable Daily Intake
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FAO	Food and Agriculture Organisation
Fpen	Market Penetration Factor
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
OECD	Organisation for Economic Co-operation and Development
OTC	Over the counter (non-prescription)
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
vPvB	Very Persistent and very Bioaccumulative
WHO	World Health Organisation

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges from MAE Holding BV.

The product is indicated for relief of symptoms of sore throat in adults and children over 6 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 lozenges which have been registered in Spain by Reckitt Benckiser Healthcare S.A. since February 1998.

The concerned member states (CMS) involved in this procedure were Czech Republic, Poland and Slovakia.

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.

Amylmetacresol and 2, 4-dichlorobenzyl alcohol are well-known active substances for the treatment of acute sore throat. Lozenges containing the combination of these two substances have been marketed as Strepsils in the Netherlands and several other member states as over-the-counter medicinal products.

II. QUALITY ASPECTS

II.1 Introduction

Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon is a yellow, biconvex, round, honey and lemon-flavoured lozenge.

Each lozenge contains:

Amylmetacresol	0.60 mg
2, 4-Dichlorobenzyl Alcohol	1.20 mg

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

The excipients are: peppermint essential oil, quinoline yellow (E104), sodium saccharin (E954), tartaric acid (E334), sunset yellow (E110), lemon essence, honey flavour, isomalt (E-953), maltitol (E965).

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.

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 was to develop a lemon and honey flavoured lozenge with 0.60 mg of amylmetacresol and 1.20 mg of 2, 4-dichlorobenzyl alcohol as drug substances. The impurity profile is comparable with the innovator. No *in vitro* study has been performed. For lozenges, there is no specific guidance. They concern a locally acting medicine with systemic activity when swallowed accidentally.

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. The product is manufactured using conventional manufacturing techniques.

Control of excipients
Quinoline yellow, yellow-orange colouring, lemon essence and honey flavour are not described in any pharmacopoeia. A specific identity test suitable for ensuring the consistency of the composition of each flavour has been established (Guideline on Excipients in the Dossier for Application for

Marketing Authorisation of a Medicinal Product, EMEA/CHMP/QWP/396951/2006) with the exception of the honey flavour. The analytical procedures and validation of the analytical procedures used for the non-compendial methods have been described and validated. The other excipients comply with the Ph.Eur. and are acceptable.

Quality control of drug product
The product specification includes tests for appearance, mean weight, uniformity of dose, drug substance identification, assay, ethanol, loss on drying, related substances and microbiological control. The release and shelf-life limits are identical for description, assay, related substances and microbiological content.
The tests for mean weight, uniformity of dose, drug substance identification and ethanol are not included in the shelf life specifications. Loss on drying is not included in the release specification. The test for related substances differs between release and shelf life specifications. Adequate release and shelf-life limits of the related substances have been set. The analytical methods have been adequately described.
Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided the same three batches stored at 25°C/60% RH (18 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. All results were within specification. The finished product was shown to be photostable, however the photostability test was not in line with the Note for guidance. A new study will be conducted post approval.
Based on the provided stability data the proposed shelf life of 30 months packed in the PVC/PVDC-Al blister without special storage condition was found acceptable. Post approval the shelf life was extended to 36 months.

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 Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitment was made:

- The MAH committed to submit a new photostability study for the active substance 2, 4-dichlorobenzylalcohol, as per the ICH Topic Q1B “Photostability Testing of New Active Substances and Medicinal Products” (CPMP/ICH/279/95).

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges contain two well-known active substances: amylmetacresol and 2, 4-dichlorobenzyl alcohol for the relief of symptoms of sore throat.
The non-clinical overview gives an adequate overview of available information on pharmacology, pharmacokinetics and toxicology for each substance apart and structurally related antiseptics, namely alcohols and phenols (including cresols).
In the Netherlands, amylmetacresol and 2, 4-dichlorobenzyl alcohol are well-known antiseptics, present in the registered Strepsils lozenges: Original (NL License RVG 04174), Lemon & Honey (RVG 06556), Orange & Vitamin C (RVG 10987), Ginger & Plum (RVG 108633), Strawberry Sugar free

(RVG 112654) and Cool (RVG 14597). These products have the same indication, posology and route of administration for adults, but there are differences for the children's indication.

Whereas the first five products are indicated for children over 6 years, Strepsils Cool (RVG 14597) is indicated for children over 12 years, because of the presence of a higher concentration menthol. Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges also contain menthol, 0.825 mg menthol in mint essential oil, but this product is indicated for children over 6 years up to a maximum dose of 4 lozenges per 24 hours.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results for amylmetacresol

Substance (INN/Invented Name): amylmetacresol			
CAS-number: 1300-94-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	log K_{ow} = 4.29 ± 0.0043	not potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{ow} = 4.29 ± 0.0043	not B
	BCF		
Persistence	ready biodegradability		
	DegT50		
Toxicity	NOEC		
	CMR		
PBT-statement :	Amylmetacresol is considered not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default and refined	0.024 (default) 0.005 (refined)	µg/L µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			N

Conclusions on studies for amylmetacresol

Amylmetacresol is considered not PBT nor vPvB. Using the refined Fpen based on prevalence data, the $PEC_{surfacewater}$ for amylcresol is below the trigger value of 0.01 µg/L for a phase II environmental risk assessment.

Summary of main study results for 2, 4-dichlorobenzyl alcohol

Substance (INN/Invented Name): 2, 4-dichlorobenzyl alcohol			
CAS-number: 1777-82-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	log K_{ow} = 2.77 ± 0.005	not potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{ow} = 2.77 ± 0.005	not B
	BCF		
Persistence	ready biodegradability		
	DegT50		
Toxicity	NOEC		
	CMR		

PBT-statement :	2, 4-dichlorobenzyl alcohol is considered not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default and refined	0.048 (default) 0.0068 (refined)	µg/L µg/L	> 0.01 threshold (Y) Refined PEC based on prevalence data and posology
Other concerns (e.g. chemical class)			N

Conclusions on studies for 2, 4-dichlorobenzyl alcohol
2, 4-dichlorobenzyl alcohol is considered not PBT nor vPvB. Using the refined Fpen based on prevalence data, the $PEC_{surfacewater}$ for 2, 4-dichlorobenzyl alcohol is below the trigger value of 0.01 µg/L for a phase II environmental risk assessment.

III.3 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. No further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

2, 4-dichlorobenzyl alcohol and amylmetacresol 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. The study is discussed below.

IV.2 Pharmacokinetics

A relative bioavailability study between the test formulation Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol strawberry lozenges (MAE Holding BV, the Netherlands) and the reference formulation Strepsils strawberry lozenges (Reckitt Benckiser Healthcare, S.A., Spain) has been submitted.

The composition of the strawberry lozenges used in the study differs from the honey & lemon lozenges only in the flavouring ingredients. These are not considered expected to influence the pharmacology of the active substances. Thus the conclusion of the *in vivo* release study using strawberry flavour lozenges can be extrapolated to the honey & lemon flavour lozenges. The choice of the reference product in the study has been justified.

Buccal release study
Design
The submitted study was a monocentric, multiple-dose, randomised, open-label, two-treatment, two-way crossover study in 44 healthy volunteers (22 females, 22 males, mean age 26±6 years).

Either a test or reference lozenge was administered daily after an overnight fasting for five consecutive days. The same formulation was administered during the five days within one period. Each administration day, the subjects received a lozenge by oropharyngeal route, which remained in the mouth a time determined by the randomisation sequence (3, 5, 8, 10 or 12 minutes). The order of time which the lozenge was held in the mouth of the subjects was the same for the two treatments. A washout period between administrations was as least 12 hours, and the washout period was 7 days between two periods.

The administration was performed in a sitting position, after wetting the mouth by rinsing and swallowing 20 mL of water. The lozenge was placed in the mouth, the volunteer was asked to not chew or move it, keeping his/her mouth closed with the lozenge in the same position. After the pre-established time, the volunteer was asked to place the remaining lozenge in an inert container, directly from the mouth, through closed lips on medication to prevent or minimize contamination with saliva. The remains of the lozenge were then diluted to obtain a matrix in which to measure the concentration of Amylmetacresol and Dichlorobenzyl Alcohol. Every lozenge was weighed before and after administration.

In this study, the release of the active substances in the mouth was measured by analysing the active substances in the remains of the lozenges at the time points. 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 two active ingredients in the medicinal products used are considered acceptable. The methods used for statistical evaluation are appropriate as well.

Results
One subject was excluded in the second period due to a positive result to opioids in the pre-administration drug test. The remaining 43 subjects completed the study and were included in the analysis.

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

Figure 1: Mean values for the dissolution profiles for Amylmetacresol

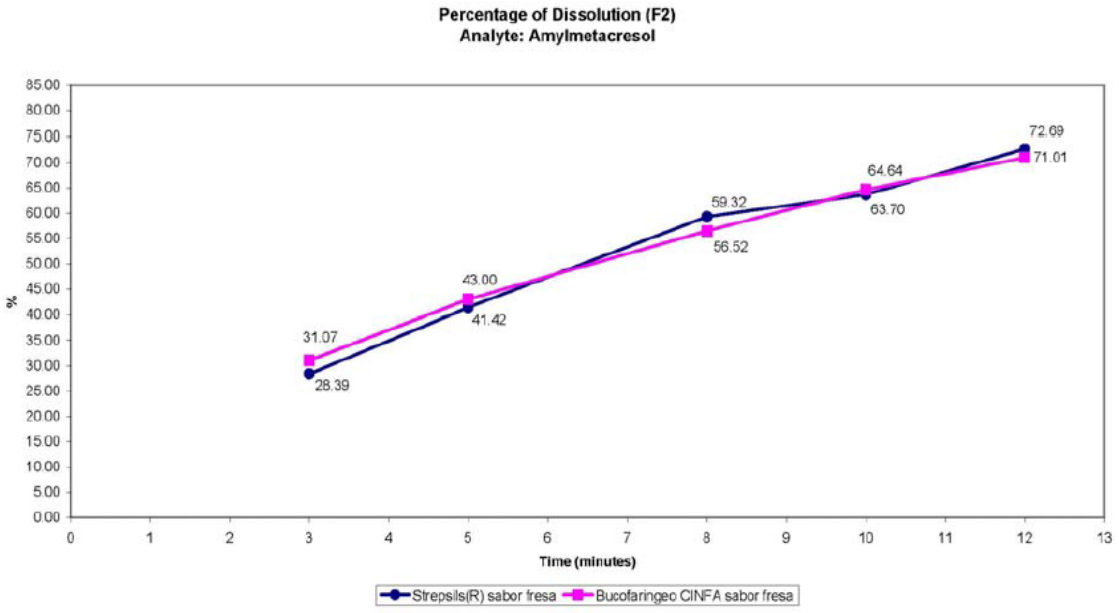
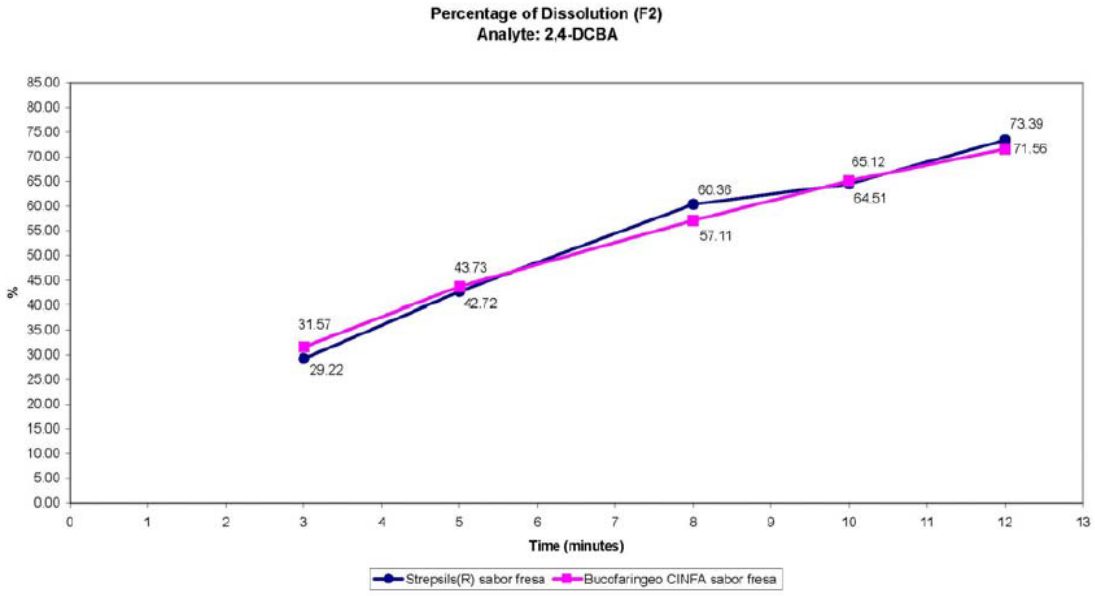


Figure 2: Mean values for the dissolution profiles for 2,4-DCBA



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.

The calculated values for the similarity factor (f2) were 83.31 for the dissolution of 2,4-dichlorobenzyl alcohol and 82.50 for amylmetacrestol.

As supportive data, mean of the total weight loss of the lozenges at every time point was calculated, which showed a comparable weight loss in percentage between test and reference product.

Study conclusion

The f2 calculation considered only the average dissolution between test and reference product, which precludes the estimation for the similarity of dissolution between products in individual subjects. In addition, as the variability in *in vivo* dissolution (30-50%) of the active substances was shown to be high at every time point for both test and reference products, the f2 value was also not accurate for concluding similarity of the products. Further parameters were considered such as the mean, the standard deviation (SD), variance of dissolution at different time points, and individual dissolution profiles for both active substances.

Based on the totality of data in this study, formulation related differences in drug release are not expected between the test and the reference product. The comparability of oral release between test and reference product is therefore considered sufficiently demonstrated.

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 Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon 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 risk		
Hypersensitivity (e.g. rash, urticaria, pruritus, mouth or pharyngeal oedema)	Routine risk minimisation Labelling SmPC section 4.3 and 4.8	None
Important potential risk		
Use in paediatric patients < 6 years	Routine risk minimisation Labelling SmPC section 4.4	None
Missing information		
Use in pregnancy and lactation	Routine risk minimisation Labelling SmPC section 4.6 and 5.3	None

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 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 active substances from the lozenges. Risk management is adequately addressed.

The SmPC is adequate for the use of this product in an OTC setting. The total amount of menthol in the lozenges, given the proposed posology, is well below the maximum acceptable daily intake. Exposure to each of the inactive ingredients is comparable to exposure from similar products that are currently marketed. It is not expected that the different amounts of excipient may alter the tolerability profile. The menthol content is considered qualified by use.

Overall, therapeutic equivalence was proven by pharmaceutical similarity and the comparative *in vivo* buccal release study. This hybrid medicinal product can be used instead of the reference product. All indications of the originator can be applied to the hybrid formulation, for adults and children over the age of six.

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 with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both test rounds all participants were able to find the correct information and answer the questions correctly.

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

Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges has a proven chemical-pharmaceutical quality and is a hybrid form of Strepsils lozeges. Strepsils is a well-known medicinal product with an established favourable efficacy and safety profile.

Buccal release of the active substances was compared in a study where the non-released amounts were assessed on several time points. The comparability of oral release between test and reference product was sufficiently demonstrated.

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 Kruidvat Amylmetacresol Plus Dichloorbenzylalcohol honey & lemon lozenges with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 December 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
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; primary packaging site; secondary packaging site	NL/H/3307/ 001/IB/001/ G	IB/G	30-8-2016	3-10-2016	Approval	N
Extension of the shelf-life of the finished product to 36 months.	NL/H/3307/ 001/IB/002	IB	4-11-2016	5-12-2016	Approval	N
Update of the CEP.	NL/H/3307/ 001/IA/004	IA	30-11-2016	13-12-2016	Approval	N