CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Strepsils Gember en Pruim bij beginnende keelpijn, lozenges Reckitt Benckiser Healthcare B.V., the Netherlands

Amylmetacresol and 2,4-Dichlorobenzyl alcohol

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 108633

29 April 2014

Pharmacotherapeutic group:	antiseptics for local oral treatment
ATC code:	R02AA03
Route of administration:	oral
Therapeutic indication:	relief of sore throat
Prescription status:	non prescription
Date of authorisation in NL:	6 February 2013
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for *Strepsils Gember en Pruim bij beginnende keelpijn,* lozenges from Reckitt Benckiser Healthcare B.V. The date of authorisation was on 6 February 2013 in the Netherlands. *Gember en pruim* means 'ginger and plum' and refers to the flavour of the lozenge.

The product is indicated for relief of sore throat.

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

In this report the product is also referred to as 'Strepsils Warm', which was the product name initially proposed, as opposed to Strepsils Cool (NL License RVG 14597).

The active substances 2,4-Dichlorobenzyl alcohol and amylmetacresol have antiseptic properties.

This national procedure concerns a line extension to *Strepsils Original bij beginnende keelpijn*, lozenges (NL License RVG 04174), which has been registered in the Netherlands by Reckitt Benckiser Healthcare B.V. since 1974. The active ingredients of Strepsils are 2,4-dichloorbenzylalcohol en amylmetacresol. The various commercially available Strepsils variants differ in excipients. With this application the MAH introduced a new flavour (ginger and plum).

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Strepsils authorisations. This information is not fully available in the public domain. Authorisations for line extensions are therefore linked to the 'original' authorised medicinal product. Reference is made to the non-clinical and clinical studies performed with Strepsils Original.

In support of this line extension, the MAH submitted one single-dose study in which the of Strepsils Warm lozenge and Strepsils Cool lozenge were compared to placebo in the relief of acute sore throat due to upper respiratory tract infections. The MAH also provided a justification for including the 'warming' flavouring agents in this new Strepsils formulation. The results of the study and the assessment of the flavouring agents are discussed in section II.3 of this report, under 'Clinical aspects' on pages 6-8.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

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
2,4-Dichlorobenzyl alcohol
The active substance 2,4-Dichlorobenzyl alcohol is an established active substance not yet described in a pharmacopoeia. The active substance is very slightly soluble in water. The molecule has no chiral centre. It is demonstrated that always the same polymorph is formed and remained during stability.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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 and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house. 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 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months). Based on the results, the proposed re-test period of 2 years when stored below 25°C was granted.

Amylmetacresol
Amylmetacresol is an established active substance described in the British Pharmacopoeia (BP*). The active substance is practically insoluble in water. The substance is a liquid at 20°C and has no chiral centre. Positional isomerism is possible, yet not observed.

The ASMF procedure is also used for this active substance.

Manufacturing process
The synthesis comprises two reaction steps. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The specifications and methods of the BP monograph on amylmetacresol are applied with additional specifications for three residual solvents. 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 several full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for one pilot-scale batch and two full-scale batches stored at 30°C/60% RH (60 months) and 40°C/750% RH (6 months). Based on the results, a re-test of 5 years when stored not above 30°C was granted.

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

Medicinal Product

Composition
Strepsils Gember en Pruim bij beginnende keelpijn is a red to purple coloured, 2.6 g, round, high-boiled lozenge, containing the active ingredients amylmetacresol at 0.6 mg per lozenge and 2,4-Dichlorobenzyl alcohol at 1.2 mg per lozenge.

The lozenges are packed in polypropylene containers with push-fit polyethylene cap or PVC/PVdC/ Aluminium blister.

The excipients are: Tartaric acid, Anthocyanins (E 163), Fruity Plum flavour, Soothing cream flavour, Warm sensation flavour, Warm Ginger spice flavour, Medium chain triglycerides, Liquid glucose and Liquid sucrose.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product is a line-extension of lozenges with identical active substances. Strepsils lozenges have been on the market for many years. Adequate information has been provided on the individual substances and the formulation. The levels of flavouring agents were determined by organoleptic trials, the aim being to achieve a distinctive, pleasant and well balanced flavour which was differentiated from the other products in the range.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The lozenges are made by a continuous process. The manufacture has been described in detail and a flow chart has been provided. The mass is mixed at high temperature and discharged continuously and cooled and finally passed into a drop forming equipment.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three consecutive manufacturing runs, each lasting one hour.

Control of excipients
For most excipients reference is made to the European Pharmacopoeia. Adequate in-house requirements have been set up for the non-compendial components. Sufficient safety information on the flavours has been provided.

Quality control of drug product
The product specification includes tests for appearance, identity (both substances), assay (both substances), degradation, average mass, uniformity of mass, and microbial purity. A limit for a degradation product is set for the shelf-life specification. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided of three pilot-scale batches stored at 25°C/60% RH (19 months), 30°/65% RH (19 months), 30°/75% RH (19 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. Photostability was investigated in the primary pack (outside of the carton) as lozenges are not intended to be stored outside of the immediate blister pack. This is acceptable. The product was demonstrated to be photostable in the blister pack. In-use stability results of the polypropylene containers did not show significant changes after 6 months.
Based on the results provided, the proposed shelf-life of 2 years and storage condition 'Do not store above 25°C' and 'Store in the original packaging' are justified.

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

This product is a line extension of Strepsils Original, which is available on the European market. 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 and pharmacokinetics data.

Toxicology
The MEB requested toxicological qualification of the flavours Fruity Plum Flavour 580306T, 050001 U30377 Soothy Cream Flavour, Flavour Sensation 506826T Hot and Warm Ginger Spice Flavour 550229TJ. These flavours are mixtures. Toxicological qualification is required to ensure that the product does not lead to an unacceptable risk in patients (children and adults).

Flavours
In addition to the pharmacologically active ingredients 2,4-dichlorobenzyl alcohol (DCBA) and amylmetacresol (AMC), the formulation of *Strepsils Gember en Pruim bij beginnende keelpijn* lozenges contains a number of excipients, all of which are safe for use in medicinal products for enteral administration.

Fruity plum flavour, soothing cream flavour, warm sensation flavour and warm ginger spice flavour are fit for human consumption as an added component of foods at the prescribed doses. All of these flavouring ingredients are classified as "GRAS" (Generally Recognized As Safe) in compliance with the US Code of Federal Regulations, Title 21, (Food & Drugs) Part 170.30 and are referred to in Parts 172, 182 and 184 of these Regulations or are present on the GRAS lists published by the Flavor and Extract Manufacturers Association (FEMA). These excipients comply with the food flavouring regulations of all countries of the European Communities and with the provisions (in particular those outlined in article 4) of the Council Directive on food flavourings (88/388/EEC). All are listed in the latest version of the European Register of flavouring substances used in or on foodstuffs, of the Commission Decision of 23 January 2002 (113/2002/EEC).

The colouring agent anthocyanins (E163) is extracted from the skins of grapes and is in full compliance with the directives of the EEC Additives No. E163 (Commission Directive 95/45/EC and any subsequent amendments); is approved by the FDA and meets the specifications outlined in the Code of Federal Regulations, Title 21, Part 73.170. The product complies with the FAO/WHO purity requirements for food additives. Liquid Sucrose is not listed in a pharmacopoeia but it is prepared by dissolving Sucrose Ph Eur in Purified Water Ph Eur.

These statements are sufficient to accept that these flavouring ingredients are safe for human consumption in the amounts used the formulation of *Strepsils Gember en Pruim* from a non-clinical point of view.

Anthocyanins are a large group of natural colours isolated from different plant species, admitted in the EU in food under registration number E163. According to the MAH, *Strepsils Gember en Pruim* contains 3.46 mg anthocyanins per lozenge. With a maximum daily dose of 12 lozenges as stated in the SmPC, the

group ADI of 2.5 mg/kg/day for anthocyanins is not exceeded for adults and children aged 6 years or older.

It has been sufficiently confirmed that the flavours are a mixture of synthetic and natural prepared flavours which do not pose an unacceptable risk to patients. All of these flavouring ingredients are classified as "GRAS" and the non-clinical overview has been adequately updated to include an assessment of the flavours.

Environmental risk assessment
The MAH performed a Phase I Environmental Risk Assessment (ERA) for core Strepsils. The active substances 2,4-Dichlorobenzyl alcohol and amylmetacresol were investigated. The results did not give rise to any concerns. Further ERA is not required.

II.3 Clinical aspects

Introduction
The active ingredients in *Strepsils Gember en Pruim bij beginnende keelpijn*, as in all Strepsils variants, are 2,4-dichorobenzyl alcohol (DCBA) and amylmetacresol (AMC). The MAH claims that these ingredients have antiseptic activity. Lozenges like Strepsils are designed to deliver the active ingredients to the inflamed throat over a prolonged period in time.

The active ingredients AMC and DCBA were shown to be released almost immediately and uniformly as the lozenge dissolved in the mouth, reaching peak concentrations within 3–4 minutes. Suggested is that the key components of pharmaceutical preparations for the treatment of sore throat, which are routinely regarded antiseptics, might have sodium channel blocking, *i.e*. local anaesthetic-like effects.

Efficacy and safety data
Berry[1] showed in his publication that a measurable benefit was obtained from the first Strepsils lozenge within 15 minutes, as demonstrated by a decrease in the mean level of throat discomfort, which appeared to reach a steady state after 45 minutes. All mean changes from baseline were significantly different from zero ($p < 0.001$).

In the publication of Wade (2008[2]) it can be seen that Strepsils lozenges provide pain relief as early as in 15 minutes, with a maximum effect after about 30 minutes and lasting for at least 2 hours. Strepsils lozenges significantly decreased mean sore throat pain intensity (*i.e.* throat soreness) compared with non-medicated lozenges in the ITT population ($p = 0.044$).

In support of the new formulation *Strepsils Gember en Pruim*, the MAH provided the results of a multicentre, randomized, double-blind, placebo-controlled, parallel-group, single-dose study investigating Strepsils Warm and Strepsils Cool versus placebo in the relief of acute sore throat due to upper respiratory tract infections (Wade *et al.* 2011[3]).In this study 225 adult patients with acute sore throat were randomly assigned to receive either one AMC/DCBA Warm lozenge (n=77), one AMC/DCBA Cool lozenge (n=74) or one unflavoured, non-medicated lozenge (matched for size, shape and demulcency; n=74). The primary efficacy variable was the Area under the Curve (AUC) in severity in throat soreness for 0-2 h on a 0-11 point scale.
Both active arms provided a significantly better relief than placebo. Additionally, both lozenge types provided relief at two hours post-dose.

Table 1 Number (%) subjects reporting each type of relief the throat lozenge provided at two hours post-dose – Full analysis set

[1] Rapid relief of acute sore throat with Strepsils lozenges: A single-blind, comparative study: P. Berry. London: Royal Society of Medicine Press; 2008.
[2].A randomised, double-blind, parallel-group, placebo-controlled, multiple-dose study of the efficacy of Strepsils lozenges in the relief of acute sore throat. AG Wade. London: Royal Society of Medicine Press; 2008.
[3] A multicentre, randomised, double-blind, single-dose study assessing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge in the relief of acute sore throat, AG Wade et al. BMC Fam Pract. 2011; vol 12:6.

Type	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
N	77	74	74		
Comforting	18 (23.4%)	19 (25.7%)	17 (23.0%)	ns	ns
Pain	18 (23.4%)	17 (23.0%)	4 (5.4%)	**	**
Soreness	19 (24.7%)	30 (40.5%)	8 (10.8%)	*	***
Relief from burning	7 (9.1%)	13 (17.6%)	5 (6.8%)	ns	*
Soothing	18 (23.4%)	32 (43.2%)	18 (24.3%)	ns	*
Coating	13 (16.9%)	10 (13.5%)	14 (18.9%)	ns	ns
Relief from swelling	6 (7.8%)	2 (2.7%)	1 (1.4%)	ns	ns
No relief	6 (7.8%)	2 (2.7%)	27 (36.5%)	***	***

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

No significant difference was observed in “relief from burning” between Strepsils Warm and placebo in contrast to Strepsils Cool. Locally applied irritating substances such as the flavoring excipients can induce pain and a burning warm sensation. Yet this observation might support the suggestion that Strepsils Warm may provide a burning sensation in the throat, which can be regarded as a signs of local irritability.
This may be masked by AMC and DCBA, the active pain relieving components of Strepils. In this study, Strepsils Warm provided soreness relief, although the effect of Strepsils Cool was better. Additionally, in contrast to Strepsils Cool, Strepsils Warm did not differ significantly from placebo on the item “soothing”.
Only a few mild to moderate adverse events (AE) have been reported that regarded non-serious AE that were only possibly related to Strepsils Warm. These observations were made after a single dose only. Signs and symptoms of local irritability will, however, often become apparent after multiple dosing for a prolonged period. Data regarding multiple dose effects were not provided. Moreover, the study design does not allow for a comparison of the efficacy of the warm and cool sensation over Strepsils original and therefore it is not possible to investigate the additional effect of the sensations “Cool” and “Warm”.

New flavour
With this line extension, the MAH applied for a new flavour under the proposed name ‘Strepsils Warm’. The MAH stated that the ingredients are used as a food additive and these can be considered safe as they are recorded in the GRAS list, which means that they are ‘Generally Recognized As Safe’. This GRAS list is an established and acknowledged enumeration of food additives that can be considered safe when used as a food additive in a normal population.
However, when ingredients are locally applied and not used as a food additive, their safety and efficacy have still to be proven. Therefore, inclusion of a certain excipient on the GRAS list does not per se prove its safety for all kinds of clinical situations.
The new mixture used in Strepsils Warm has been composed to provide a warmth sensation because patients may associate warmth with relief of pain and discomfort. It contains capsicum oleoresin, a plant extract. The active component of the warm sensation flavour is capsaicin, the active component of chili peppers. This ingredient may be harmful when applied on a (damaged) mucus membrane or inflamed skin. Strepsils lozenges are designed to increase the exposure to the ingredients in the throat in order to provide a “warm” sensation.
In addition, the comparability of the “warmth sensation” provided by a warm drink or by a mixture of ingredients can be disputed. Therefore inclusion of claims regarding a “warming effect” are not considered appropriate. The MEB considered that further investigation was required on the GRAS status of the ingredients.

The indication for Strepsils warm is symptomatic relief in acute sore throat. The name “Warm” is chosen to refer to an additional sensation to smoothen a sore throat. In the previous round, the name of Strepsils *Warm* was rejected, because the name suggests a warming sensation which is caused by an excipient and not by an active substance. The Board regarded this name confusing and not allowed on procedural grounds.

Discussion and benefit/risk assessment
Because of these serious objections the MAH was invited for a hearing. In this hearing, the MAH responded to the objections raised by the MEB:

- Product name

With regard to the product name, the Board argued that including ‘Warm’ is not acceptable, as this does not concern a therapeutic effect of the active substances. The MAH therefore revised the product name to *Strepsils Gember en Pruim bij beginnende keelpijn.*

- Tolerability of flavouring agents

The Board considered the provided data (a single dose study concerning local irritability) insufficient, as signs of irritability usually become clear after multiple dosing. Data regarding multiple dose effects were not provided. The MAH did not substantiate that the submitted safety data as food additive (classification as GRAS in compliance with the US code of Federal Regulations) can be extrapolated to topical use. The MEB noted that the “warm” flavours (*i.e*. Warm Ginger Spice flavour 550229 TH and Warm Sensation flavour 506826 T) contain irritating ingredients like capsicum oleoresin, which may be harmful when applied on (damaged) mucus membrane. Finally the anticipated population is patients with an inflamed throat, in general patients with inflamed mucosa are more sensitive to irritable effects.

In their response, the MAH submitted certificates which confirm that the flavouring mixtures Warm Sensation flavour and Warm Ginger Spice flavour have a GRAS status.
A calculation was made which indicates that the capsaicin containing component in Strepsils Warm, capsicum oleoresin, will result in an intake of 0.04 mg capsaicin/24 hrs when taking 12 lozenges per 24 hours. The Committee of Experts on Flavouring Substances laid down a temporary maximum daily intake (TMDI) of 0-0.2 mg capsaicin per kg body weight/24 hrs, based on “the rough assumption of low toxicity for oral doses of 4 mg capsaicinoids/kg body weight in humans and using a safety factor of 20”. This means that at a body weight of 60 kg, a TMDI of 12 mg/24 hrs is reached. This means a safety margin of 300 with capsaicin intake through lozenges.

Strepsils Warm has been registered in 27 countries with an OTC status. The MAH stated that more than 125 million packs of Strepsils Warm have been sold since august 2010. The MAH provided data to demonstrate that no safety issues appeared in the post marketing surveillance, which is considered reassuring, although underreporting of adverse events is notorious in post marketing surveillance. The amount of reported adverse events was however comparable between Strepsils Original and Strepsils Warm.

The MAH decided to limit the maximum recommended duration of use for all Strepsils variants from 14 to 3 days, in the context of a harmonization procedure for <u>all</u> Strepsils variants due to an harmonization procedure for all European countries. In case of Strepsils Warm, this will reduce the possible cumulative effects of local intolerability. The pack size will be in line with the approved posology*, i.e.* ≤ 36 lozenges per pack. The statement “occasional hypersensitivity reactions” in section 4.8 of the SmPC for all Stepsils variants will be adapted to “occasional hypersensitivity reactions may occur including rash, a feeling of burning or tingling and oedema of the mouth or throat”.

<u>Conclusion</u>
Based on the above data and further justifications, the Board considers that the safety of Strepsils ‘Warm’ is sufficiently warranted. The safety margin for intake of capsaicin, which is used as a flavouring agent, is sufficiently large. The MAH agreed to adapt the product name, as inclusion of ‘warm’ in the product name is not acceptable. As for the other Strepsils products, the new variant can be granted a non-prescription, ‘over-the-counter’ status (general sales).

Risk management plan
The MAH did not provide a separate Risk Management Plan for this product, as the active ingredients are well established in combination. Consequently, the risk associated with the product is low and the Board reckons the Pharmacovigilance system in place will adequately address any anticipated risks for the product. The absence of a separate RMP is acceptable.

Product information

SmPC
The content of the SmPC approved during the national is largely in line with those for the other Strepsils products and has been adequately adapted in line with the Board's comments.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the applicable European Directives. The test was conducted in Dutch and consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. A readability test consists of a number of personal interviews, using a structured questionnaire. The questions address the key issues regarding safe and effective use of the medicine. The purpose of a readability test is to determine whether test participants can find specific information in a leaflet, understand the information they have found, and whether they would act appropriately.
After the pilot round some textual revisions were made to the PL; these proved to be sufficient and after the first and second test rounds no further changes were considered necessary. During the first test round 99% of the questions, and in the second test round 100% of the questions were answered correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Strepsils Gember en Pruim bij beginnende keelpijn, lozenges has a proven chemical-pharmaceutical quality and is an approvable line extension to Strepsils Original lozenges, which is a well-known medicinal product with an established favourable efficacy and safety profile.

In support of this new variant, the MAH submitted the results of one single-dose study, comparing Strepsils Warm and Strepsils Cool to placebo in patients with acute sore throat due to upper respiratory tract infections. Relief of throat soreness with Strepsils was demonstrated to be significantly better than with placebo.

The Board thoroughly considered the data provided by the MAH, particularly with regard to the safety and tolerability of the flavouring agents in the new formulation.
The MAH provided certificates which confirm that the flavouring mixtures Warm Sensation flavour and Warm Ginger Spice flavour have a GRAS status. Concerns with regard to the “warm” flavours have been sufficiently addressed. Moreover, the MAH limited the duration of use for Strepsils to a maximum of 3 days, instead of the 2 weeks initially proposed. Safety data from post marketing experience with Strepsils ‘Warm’ do not indicate specific safety concerns compared to Strepsils Original.

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

The SmPC, package leaflet and labelling cover appropriate information and are in the agreed templates. The product was acceptably renamed, as ‘Warm’ does not refer to a therapeutic effect of the active substances and is not acceptable for inclusion in the product name.

Overall, based on the dossier submitted, the Board considers that efficacy and safety has been sufficiently proven and has therefore granted a marketing authorisation. *Strepsils Gember en Pruim bij beginnende keelpijn*, lozenges was authorised in the Netherlands on 6 February 2013.

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

List of abbreviations

ADI	Acceptable Daily Intake
AE	Adverse Event
AMC	Amylmetacresol
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
AV	Algemene Verkoop (general sales)
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
DCBA	2,4-dichorobenzyl alcohol
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FAO	Food and Agricultural Organization
FEMA	Flavor and Extract Manufacturers Association
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognized As Safe
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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TMDI	Temporary Maximum Daily Intake
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached Y/N
Introduction of the Pharmaco-vigilance System Master File (PSMF).	IA	19-3-2013	18-4-2013	Approval	N
Addition of a CEP which is newly approved by the EDQM for the already approved active substance manufacturer.	IA	6-1-2014	5-2-2014	Approval	N
Change of the AMC specification to comply with the European Pharma-copoeia	IA	6-1-2014	5-2-2014	Approval	N