CBG MEB

Public Assessment Report

Scientific discussion

Strepsils Aardbei Suikervrij bij beginnende keelpijn, lozenges

(2,4-Dichlorobenzyl alcohol and amylmetacresol)

NL License RVG: 112654

Date: 13 April 2015

This module reflects the scientific discussion for the approval of *Strepsils Aardbei bij beginnende keelpijn*, lozenges. The marketing authorisation was granted on 15 May 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for *Strepsils Aardbei Suikervrij bij beginnende keelpijn*, lozenges from Reckitt Benckiser Healthcare B.V. *Aardbei* means 'strawberry´ 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.

This national procedure concerns the application for a new variant of Strepsils. The MAH initially proposed the name *Strepsils Aardbei Kinderen*. The first registered product was Strepsils Original bij beginnende keelpijn, lozenges (NL License RVG 04174), authorised in the Netherlands by Reckitt Benckiser Healthcare B.V. since 1974. The active ingredients of Strepsils are ,4-Dichlorobenzyl alcohol and amylmetacresol. The various commercially available Strepsils variants differ in excipients.
In *Strepsils Aardbei Suikervrij* the sugar content is replaced by artificial sweetener (isomalt and maltitol), and a new flavour is introduces (strawberry).

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

The MAH provided a justification for including the flavouring agents in this new formulation, and justified that the artificial sweeteners may contribute to the soothing effect of S*trepsils Aardbei Suikervrij*.

II. QUALITY ASPECTS

II.1 Introduction

Strepsils Aardbei Suikervrij bij beginnende keelpijn is a pink, circular lozenge with the brand icon intagliated on both sides.

The lozenge contains 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 PVC/PVdC/Aluminium blisters.

The excipients are: strawberry flavour 052312B, Pink antho P-WS (E163), sodium saccharin, tartaric acid, liquid maltitol (E965) and isomalt (E953).

II.2 Drug 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.

<u>Manufacturing process</u>

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.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Existing sugar free products with similar formulation details have been marketed in Europe and around the world for many years.
In the Strepsils sugar free formulation the sucrose and glucose content of the lozenge is replaced with isomalt and maltitol. The product contains no novel excipients. The level of Flav P Strawberry Flavour 052312B was determined by organoleptic trials. The colourant is an approved food additive and conforms to the directive 95/45/EC.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The lozenges are made by a continuous process, i.e. continuous lozenge base production. Amylmetacresol and 2,4-Dichlorobenzyl benzylalcohol are metered in at a rate proportional to the flow rate of the lozenge mass.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches.

Control of excipients
For most excipients reference is made to the Ph.Eur. In-house specifications have been set for the flavour and the colorant. These specifications are acceptable. Compliance for the colourant and flavouring with the EC Directive on food additives has been stated.

Quality control of drug product
The product specification includes tests for description, identification of both drug substances, average mass, uniformity of mass, assay, water activity and microbiological tests. The release and shelf life specifications are similar with the exception that uniformity of content has been included in the shelf life specification and not in the release specification. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches.

Stability of drug product
Stability data on the product has been provided for three production-scale batches stored at 25°C/60% RH (18 months), 30°/65% RH (18 months), 30°C/75% RH (18 months) and 40°C/75% RH (39 weeks). Furthermore a photostability study was performed on all three batches. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed PVC/PVdC-Al packaging.
The stability results show that at accelerated conditions out-of-specification results were observed for appearance after 26 weeks. All other results complied and other trends have not been observed. The product did not change during the photostability study.
Based on the results provided, the claimed shelf life of 2 years in PVC/PVdC-Al blister; 'Do not store above 25°C.' is 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 MEB considers that *Strepsils Aardbei Suikervrij bij beginnende keelpijn*, lozenges has 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 Introduction

This product is new variant 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.

III.2 Toxicology

Strepsils Aardbei Suikervrij lozenges contain 9 mg Strawberry Flavour 052312 B per lozenge (0.39%). The flavour consists of 46 components, comprising flavouring substances and flavouring preparations. Most of the flavouring substances are present on the Union List implemented by Regulation 872/2012. For this reason, these substance are qualified.
However some of the flavouring preparations are not present on the Union List. In addition, it should be noticed that spices and herbal preparations are also not covered by REGULATION (EC) No 1334/2008. The MAH demonstrated that Firmenich Strawberry flavour 052312 B is not a novel excipient, and in use as excipient in a registered medicinal product in one of the EU Member States. The MAH provided also documentation that Strepsils lozenges, in the formulation containing Strawberry Flavour 052312 B, have been licensed in a large number of EU countries.
The MAH further referred to the EU regulation on flavouring preparations stating that preparations produced from food do not need to undergo an evaluation or an approval procedure for use in and on foods unless there is doubt about their safety.
Public information does not point to safety concerns of these ingredients

III.3 Ecotoxicity/environmental risk assessment (ERA)

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.

III.4 Discussion on the non-clinical aspects

The preclinical safety of the active ingredients is considered established. No new studies were required. It has been sufficiently confirmed that the flavours are a mixture of ingredients which do not pose an unacceptable risk to patients. All of the flavouring ingredients can be regarded as safe.

IV. CLINICAL ASPECTS

IV.1 Introduction

The active ingredients in *Strepsils Aardbei Suikervrij 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.

IV.2 Efficacy and safety

In the current application, the glucose is replaced by the artificial sweeteners (mannitol, isomalt). It is not demonstrated whether artificial sweeteners have a similar effect on the salivary production as sugar. This was an important discussion point during the evaluation. No literature has been provided demonstrated that the artificial sweetener has a comparable effect to sugar (sucrose). Clinical data with *Strepsils Aardbei Suikervrij* is lacking.
A total of seven trials have been conducted to compare the *in vivo* effects of Strepsils lozenges. Only the studies assessing the effect of Strepsils Original are considered relevant in the current application, because the addition of other active substances may have induced additional effects.
The local anaesthetic-like effects of Strepsils Original has been compared in two randomized double blind studies with sucrose-glucose placebo (TH0705 and BH501BR). In only one of the two studies, a statistically significant effect over placebo was observed in the primary outcome.

No evidence is provided to demonstrate the efficacy of *Strepsils Aardbei Suikervrij* or other Strepsils in which sugar was replaced by isomalt, maltitol or other sugar-replacing ingredients. This is deemed important, because the pain relieving effect of Strepsils Original might partly be attributed to the lubricating effect of sugar. Evidence suggests that sapid substances like sugar will increase reflex salivation and may also promote secretion of airway mucus. In addition, sugar may generate endogenous opioids. Therefore, the MEB doubted if Strepsils without sugar might have the same efficacy as sugar-containing Strepsils lozenges.
The comparable dissolution times, submitted as evidence of comparable efficacy between Strepsils sugared lozenges and Strepsils Sugarfree lozenges, are considered to indicate only similar efficacy of the active substances AMC and DCBA but not for the potential change (loss) of activity by the replacement of the sugars. The clinical effect of the substitution of glucose and sucrose by maltitol and isomalt cannot be determined with this method.

The MAH provided review articles which stated that lozenges increase salivary flow and relieve the pain in the throat by lubricating the mucosa[1]. The use of candy containing artificial sweeteners is recommended as a means of stimulating extra salivary flow to aid caries management[2]. In addition reference was made to an old article, which states that a higher flow rate of saliva was observed in subjects using sugarless gum compared to those using sugar containing gum[3].

There is no clinical evidence that artificial sweeteners have a similar effect on the salivary production as sugar. However, indirect evidence was provided that artificial sweeteners may stimulate the salivary flow as well. The artificial sweeteners therefore may contribute to the soothing effect of *Strepsils Aardbei Suikervrij*.

Given the availability of Strepsils exposure for decades, there is sufficient evidence that Strepsils have no unfavourable effects. No important safety issues were further identified.

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 *Strepsils Aardbei Suikervrij*.

Summary of the safety concerns

Important identified risks	Hypersensitivity (eg. Rash, urticaria, pruritus)
Important potential risks	None
Missing information	None

The MEB 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 original Strepsils dossier. No new clinical studies were conducted. The MAH demonstrated based on literature that the sugarfree formulation is not likely to impact efficacy of the Strepsils lozenge. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. Reference was made to the successfully user tested PL for *Strepsils Gember en Pruim bij beginnende keelpijn*, lozenge (RVG 108633). The MAH has shown that the two leaflets are highly similar. Therefore, bridging is accepted. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Strepsils Aardbei Suikervrij bij beginnende keelpijn, lozenges has a proven chemical-pharmaceutical quality and is an approvable addition to the registered Strepsils. Strepsils which is a well-known medicinal product with an established favourable efficacy and safety profile.

[1] Genrali JA: Drug Form U.SS. Pharm 1987; 12: 3-26
[2] Humphrey SP, Williamson RT. A review of salvia, normal composition , flow and function. J Preostet Dent 2001; 85:162-9
[3] Shannon IL, Frome WJ. J Can Dent Assoc 1973; 39(3):177-81

In support of this new variant, the MAH submitted non-clinical and clinical literature. The excipients are considered safe. The positive effect of Strepsils is believed to be due to both the active ingredients AMC/DHCBA and the salivary production. The artificial sweeteners in *Strepsils Aardbei Suikervrij* may stimulate salivary flow.

The Board followed the advice of the assessors. The MEB considered that the name *Strepsils Aardbei kinderen* should be changed, because the use of the lozenge is not limited to children. The MAH agreed.

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 Aardbei Suikervrij bij beginnende keelpijn*, lozenges was authorised in the Netherlands on 15 May 2014.

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
Change in the name of the medicinal product.	IB	31-10-2014	19-11-2014	Approval	No