COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Strepfen Orange Sugar free 8.75 mg, lozenges (flurbiprofen)

NL/H/4698/001/DC

Date: 8 February 2022

This module reflects the scientific discussion for the approval of Strepfen Orange Sugar free 8.75 mg, lozenges. The procedure was finalised on 29 September 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Strepfen Orange Sugar free 8.75 mg, lozenges, from Reckitt Benckiser Healthcare B.V.

Strepfen Orange Sugar free is indicated for the short term symptomatic relief of sore throat in adults and adolescents over the age of 12 years.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the reference product Strefen Lozenges (Reckitt Benckiser Healthcare, Scandinavia A/S), authorised on 4 July 2008 in Denmark. The reference product was authorised via procedure UK/H/0388 (now NL/H/4456). The former reference member state (United Kingdom) confirmed that UK/H/0388/001 was authorised on the basis of a full dossier; the product of Denmark is therefore suitable to be considered as a reference medicinal product.

In the Netherlands, the reference product Strepfen Orange Sugar free 8.75 mg, lozenges (NL RVG 109114) has been registered since 31 July 2012 by procedure NL/H/4615/001 (former UK/H/4701).

A European Reference Product is used in concerned member states (CMS) Germany and Slovakia: Strepsils Intensive Orange Sugar Free 8.75mg Lozenges, Reckitt Benckiser Ireland Ltd., registered in Ireland in 2014. The justification to use this product is based on information received from Ireland. The ERP information received from Ireland was circulated during validation period.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, Croatia, Hungary, Iceland, Luxembourg, Latvia, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovakia.

Legal base

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as bioavailability studies cannot be used to demonstrate bioequivalence, as the product has some local action. However, therapeutic equivalence is established between the products as both the product being applied for and the reference product have identical formulations and are manufactured in the same factory to the same manufacturing process and controls. A comparative bioavailability study is included in this application.

II. QUALITY ASPECTS

II.1 Introduction

Strepfen Orange Sugar free is a round, white to pale yellow lozenge with an icon intagliated on both sides of the lozenge.

The product contains as active substance 8.75 mg of flurbiprofen.

The lozenges are packed in an opaque PVC/PVdC/Al blister.

The excipients are: macrogol 300, potassium hydroxide (E525), orange flavour (contains flavouring substances, triacetin, citral, citronellol, d-limonene, geraniol and linalool), levomenthol, acesulfame potassium (E950), liquid maltitol (E965) and isomalt (E953).

II.2 Drug Substance

The active substance is flurbiprofen, an established active substance described in the European Pharmacopoeia. The active substance is a white or almost white, crystalline powder and is practically insoluble in water, but freely soluble in alcohol and in methylene chloride. It dissolves in aqueous solutions of alkali hydroxides and carbonates.

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 Ph.Eur.

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 is in line with the CEP. 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 scaled batches

The active substance is stable for three years when stored in fibreboard drums lined with two polyethylene bags, and protected from light. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

Stability of drug substance
The active substance is stable for three years when stored in fibreboard drums lined with two polyethylene bags, and protected from light. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The MAH has confirmed that the product and dossier are identical to that of the originator product already authorised in the Netherlands (NL/H/4615 (former UK/H/4701)). The information contained is representative of this type of application: an already existing product where both the existing product and the product applied for have the same formulation, manufacturing process and controls.

Compatibility studies have been provided for the several excipients in combination with the active substance.

Manufacturing process
The manufacture of the lozenges is a continuous manufacturing process. The isomalt, liquid maltitol, acesulfame potassium and purified water are continuously combined in fixed ratios. The flurbiprofen solution and flavour solution are dispensed by suitable dosing pumps which ensure that all components are dosed in the correct proportion. These solutions are fed directly into the mixing system where they are mixed with the lozenge base. The lozenge mass passes continuously into suitable lozenge forming equipment and the subsequently formed lozenges are transferred onto a conveyor. The cooled lozenges are then collected in suitable containers and labelled with an identifying number.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches.

Control of excipients
The excipients comply with Ph. Eur. requirements. For the orange flavour an in-house specification is provided. These specifications are acceptable.

Microbiological attributes
The finished product will be manufactured under Good Manufacturing Practices conditions using a manufacturing process involving high temperatures, providing assurance that the microbiological quality of the lozenges will be satisfactory at the time of manufacture.

The reference product has been tested for water activity during stability testing and confirmed that the result are at a level at which the product will not support microbiological growth. Microbiological testing will be carried out on one batch per year to ensure that manufacturing control is maintained.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity of active substance, average mass, uniformity of mass, uniformity of dosage units, assay, related substances and microbiological tests. The requirements for the parameters do not differ between release and shelf-life specifications, except for description. Slight change in colour of the lozenges may occur. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Suitable risk evaluation for nitrosamine impurities and elemental impurities in the product are provided. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60% RH (36 months), 30°C/65% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in opaque PVC-Al blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are: “Do not store above 25°C.

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 Strepfen Orange Sugar free has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- As agreed during the procedure, the MAH commits to varying the name and flavour registered on the licence prior to launch of the product. The names of the product will be varied according to national requirements in each market.
- The MAH commits to provide the report from the forced degradation study for the finished product, following a request from a CMS.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Strepfen Orange Sugar free is intended for substitution of a similar product available at the European market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Strepfen Orange Sugar-free which is available on the European market. 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

Flurbiprofen is a well-known active substance 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.

In principle, according to the current requirements, and considering that the efficacy of flurbiprofen lozenges is due to local effects of the drug, a local availability study as a surrogate for efficacy is normally required for this type of hybrid application. However, since this proposed product is also the originator product and is registered since 2012, no new data was requested, since the MAH could confirm that the currently provided module on quality is almost identical to the module on quality in the dossier of the currently approved originator product. Both the existing product and the product applied for in this application have the same formulation, manufacturing process and controls. The MAH clarified that differences exist due to a change in the name of the flavour component. The change of

flavour is in the name only, and does not affect the efficacy of flurbiprofen lozenges and has no impact on the bioavailability. To demonstrate that the changes in formulations do not alter the pharmacokinetic parameters of the lozenges, a bioavailability study with four test formulations was performed, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Strepfen Orange Sugar free 8.75 mg, lozenges (Reckitt Benckiser Healthcare B.V., The Netherlands) is compared with the pharmacokinetic profile of the originator product Flurbiprofen 8.75 mg sugar cherry (liquid flavour) lozenge (Reckitt Benckiser Healthcare B.V., Italia).

The bioavailability study has been considered as a good measure of equivalence for this medicine as whilst it's action is topical, it will also have a systemic component. The systemic absorption of flurbiprofen from such formulations is well demonstrated and reproducible, and when it can be systemically absorbed through the mucus membranes around the area of effect (the throat) then local tissue penetration can also be expected. No new data has been submitted during the current procedure, which has been justified.

IV.2.1 Bioequivalence study

Design

A open-label, five-way crossover, randomised, single dose, comparative bioequivalence study was carried out under fasted conditions in 20 healthy subjects, aged 18-50 years. Each subject received a single dose (8.75 mg) of one of five flurbiprofen formulations. The different formulations were:

- A: Flurbiprofen 8.75mg sugar cherry (liquid flavour) lozenge (**reference product**)
- B: Flurbiprofen 8.75mg sugar cherry (powder flavour) lozenge
- C: Flurbiprofen 8.75mg Sugar free orange (powder flavour) lozenge
- D: Flurbiprofen 8.75mg Sugar free orange lozenge (**current test product**)
- E: Flurbiprofen 8.75mg sugar honey and lemon lozenge

The tablet was orally administered after a fasting period of ten hours. Subjects were instructed to suck the lozenge, and to refrain from chewing or crunching the lozenge. There were five dosing periods, separated by a washout period of two to five days. Blood samples were collected at 5, 10, 15, 30, 45, 60, 75, 90, 120, 180, 240, 360, 480 and 720 minutes after administration of the products. The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Out of the 20 subjects, one subject withdrew from the study via withdrawal of consent. 19 subjects were eligible for pharmacokinetic analysis. In this paragraph, only the relevant results for this procedure are discussed, namely the pharmacokinetic parameters of the reference product A and test product D. The results of the flurbiprofen pharmacokinetic analyses of the primary endpoints, provided as geometric means, test to reference ratios and associated 97.5% confidence intervals are presented in Table 1.

Table 1. Pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (geometric LS means), t_{max} and $t_{1/2}$ (median) of flurbiprofen under fasted conditions.

Treatment N=19	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	5681.26	6192.79	1616.13	45.0	3.19
Reference	6008.62	6594.59	1618.12	45.0	3.26
***Ratio (97.5% CI)**	0.946 (0.893 – 1.001)	0.939 0.885 – 0.997	0.999 0.911 – 1.095	--	--

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
97.5% CI	97.5% confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:

The 97.5% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, the product Strepfen Orange Sugar free 8.75 mg, lozenges is considered bioequivalent with Flurbiprofen 8.75mg sugar cherry (liquid flavour) lozenge.

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

IV.3 Clinical efficacy and safety

Extensive clinical experience with flurbiprofen is considered to have demonstrated therapeutic value of the compound for the short term symptomatic relief of sore throat. The efficacy of flurbiprofen 8.75mg lozenges is well-established and does not require further evaluation with controlled clinical studies. As this application concerns a hybrid application for flurbiprofen 8.75 mg orange Sugar free lozenges, no new clinical efficacy data is included as the efficacy of flurbiprofen 8.75 mg lozenges is well established.

An overview is provided of several clinical studies which have been performed previously with mainly 8.75 mg flurbiprofen lozenges. These studies include:

- One dose ranging study, which compared the efficacy of 2.5 mg, 5 mg and 12.5 mg flurbiprofen lozenges to placebo (Schachtel et al., 2002).
- Six placebo-controlled studies that assessed the efficacy of flurbiprofen 8.75 mg lozenge:
  - Watson et al. (2000);
  - Benrimoj et al. (2001);
  - Blagden et al. (2002);
  - Schachtel et al. (2014a), Shephard. et al (2015), Aspley et al. (2016), Schachtel et al. (2016);
  - Schachtel et al. (2014b), Shephard et al. (2015);
  - Schachtel et al. (2018a & 2018b).
- One non-inferiority study in which a flurbiprofen 8.75 mg spray was compared to the flurbiprofen 8.75 mg lozenge (Burova et al., 2018; Radkova et al., 2017).
- One open-label comparative study in which flurbiprofen 8.75 mg lozenge was compared to 1 gram paracetamol (Sedinkin et al., 2005).

The published efficacy studies demonstrate significant clinical benefits of flurbiprofen 8.75 mg lozenge compared to placebo in relieving symptoms associated with sore throat. Flurbiprofen 8.75 mg lozenge was more effective than placebo in providing pain relief and relieving throat soreness, throat pain, difficulty swallowing and swollen throat after single and multiple doses. Recent studies on the flurbiprofen 8.75 mg lozenge have also provided a better understanding of the time of onset and duration of clinical efficacy. Demulcent action was detected at 2-minutes with first perceivable relief within 15 minutes and meaningful relief achieved within the hour following dosing. The median time to meaningful relief was consistent with those observed for systemic analgesics (Schachtel et al., 2018a). Statistically significant reductions in pain, difficulty in swallowing, and the sensation of a swollen throat over placebo are evident. These statistically significant separations from placebo represent differentiation from demulcent effects and progression to nociceptive pharmacologic activities rather than just separation of active drug from inactive placebo. Differences observed substantiate a clinically meaningful change. Results do not differ significantly in patients with streptococcal throat infection and supports the use of symptomatic treatment until culture results indicate a bacterial infection.

The safety of flurbiprofen 8.75 mg lozenges is well-established and does not require further evaluation by controlled clinical studies.

IV.4 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 Strepfen Orange Sugar free.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient to identify and characterise new risks.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product . No new clinical studies were conducted. Therapeutic equivalence is established between the products as both the product being applied for and the reference product have identical formulations and are manufactured in the same factory with the same manufacturing process and controls. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to currently approved Streflam Lozenges (Reckitt Benckiser International Ltd). Since the approval of this reference product the leaflet of the reference product has changed several times through the submission and approval of variations. None of these variations have required updated user testing to be carried out, the submitted user test report is considered still supportive of the current version of the reference product leaflet. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Strepfen Orange Sugar free 8.75 mg, lozenges has a proven chemical-pharmaceutical quality and is a hybrid form of the currently approved Strepfen Orange Sugar free 8.75 mg, lozenges. Strepfen lozenges is a well-known medicinal product with an established favourable efficacy and safety profile. Therapeutic equivalence is established between the products as both the product being applied for and the reference product have identical formulations and are manufactured in the same factory to the same manufacturing process and controls.

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 Strepfen Orange Sugar free with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 September 2021.

VII. REFERENCES

Aspley, S., Shephard, A., Schachtel, E., Sanner, K., Savino, L., & Schachtel, B. (2016). Efficacy of flurbiprofen 8.75 mg lozenge in patients with a swollen and inflamed sore throat. *Current medical research and opinion*, *32*(9), 1529–1538. https://doi.org/10.1080/03007995.2016.1187119

Benrimoj, S. I., Langford, J. H., Christian, J., Charlesworth, A., & Steans, A. (2001). Efficacy and Tolerability of the Anti-inflammatory Throat Lozenge Flurbiprofen 8.75mg in the Treatment of Sore Throat : A Randomised, Double-Blind, Placebo-Controlled Study. *Clinical drug investigation*, *21*(3), 183–193. https://doi.org/10.2165/00044011-200121030-00004

Blagden, M., Christian, J., Miller, K., & Charlesworth, A. (2002). Multidose flurbiprofen 8.75 mg lozenges in the treatment of sore throat: a randomised, double-blind, placebo-controlled study in UK general practice centres. *International journal of clinical practice*, *56*(2), 95–100.

Burova, N., Bychkova, V., & Shephard, A. (2018). Improvements in throat function and qualities of sore throat from locally applied flurbiprofen 8.75 mg in spray or lozenge format: findings from a randomized trial of patients with upper respiratory tract infection in the Russian Federation. *Journal of pain research*, *11*, 1045–1055. https://doi.org/10.2147/JPR.S149331

Radkova, E., Burova, N., Bychkova, V., & DeVito, R. (2017). Efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection: a randomized, non-inferiority trial in the Russian Federation. *Journal of pain research*, *10*, 1591–1600. https://doi.org/10.2147/JPR.S135602

Schachtel, B. P., Homan, H. D., Gibb, I. A., & Christian, J. (2002). Demonstration of dose response of flurbiprofen lozenges with the sore throat pain model. *Clinical pharmacology and therapeutics*, *71*(5), 375–380. https://doi.org/10.1067/mcp.2002.124079

Schachtel, B., Aspley, S., Shephard, A., Shea, T., Smith, G., Sanner, K., Savino, L., Rezuke, J., & Schachtel, E. (2014a). Onset of action of a lozenge containing flurbiprofen 8.75 mg: a randomized, double-blind, placebo-controlled trial with a new method for measuring onset of analgesic activity. *Pain*, *155*(2), 422–428. https://doi.org/10.1016/j.pain.2013.11.001

Schachtel, B. & Shephard, Adrian & Aspley, Sue & Smith, Gary. (2014b). (116) SPID2 and SPID24 in the evaluation of acute analgesics taken episodically. The Journal of Pain. 15. S5. 10.1016/j.jpain.2014.01.022.

Schachtel, B. P., Shephard, A., Shea, T., Sanner, K., Savino, L., Rezuke, J., Schachtel, E., & Aspley, S. (2016). Flurbiprofen 8.75 mg lozenges for treating sore throat symptoms: a randomized, double-blind, placebo-controlled study. *Pain management*, *6*(6), 519–529. https://doi.org/10.2217/pmt-2015-0001

Schachtel, B., Aspley, S., Shephard, A., Schachtel, E., Lorton, M. B., & Shea, T. (2018). Onset of analgesia by a topically administered flurbiprofen lozenge: a randomised controlled trial using the double stopwatch method. *British journal of pain*, *12*(4), 208–216. https://doi.org/10.1177/2049463718756152

Schachtel, B., Shephard, A., Schachtel, E., Lorton, M. B., Shea, T., & Aspley, S. (2018). Qualities of Sore Throat Index (QuaSTI): measuring descriptors of sore throat in a randomized, placebo-controlled trial. *Pain management*, *8*(2), 85–94. https://doi.org/10.2217/pmt-2017-0041

Sedinkin, A. A., Balandin, A. V., & Dimova, A. D. (2005). *Terapevticheskii arkhiv*, *77*(3), 74–76.

Watson, N., Nimmo, W. S., Christian, J., Charlesworth, A., Speight, J., & Miller, K. (2000). Relief of sore throat with the anti-inflammatory throat lozenge flurbiprofen 8.75 mg: a randomised, double-blind, placebo-controlled study of efficacy and safety. *International journal of clinical practice*, *54*(8), 490–496.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse