COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Flurbiprofen Healthypharm 8.75 mg lozenges sugar-free (orange) (flurbiprofen)

NL/H/5992/001/DC

Date: 4 November 2025

This module reflects the scientific discussion for the approval of Flurbiprofen Healthypharm 8.75 mg lozenges sugar-free (orange). The procedure was finalised on 6 August 2025. 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
EMA	European Medicines Agency
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 Flurbiprofen Healthypharm 8.75 mg lozenges sugar-free (orange), from Healthypharm B.V.

The product is indicated for: the local short-term symptomatic relief of sore throat in adults and adolescents over the age of 12 years.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application as it relies in part on the results of pre-clinical bioequivalence tests and clinical trials of chosen reference products and in part on new data. The reference products have the same Global Marketing Authorisation, as they belong to the same MAH, contain the same amount of active substance, have the same pharmaceutical form and the same method of administration.

In this decentralised procedure, therapeutically equivalence is proven between the new product and the innovator product Strepfen (NL RVG 101477) which has been registered in the UK by Crookes Healthcare Limited since 2001 (original product). In the Netherlands, Strepfen Citroen & Honing 8,75 mg, zuigtabletten has been registered since 2010 by the procedure NL/H/4456.

The concerned member state (CMS) involved in this procedure was Germany.

II. QUALITY ASPECTS

II.1 Introduction

Flurbiprofen is a round orange lozenge. It contains as active substance 8.75 mg of flurbiprofen.

The excipients are: isomalt (E953), maltitol liquid (E965), potassium acesulfame (E950), macrogol 300 (E1521), potassium hydroxide (E525), cochineal Red A (E124), sunset yellow FCF (E110), orange flavour (limonene, decanal, citral, citronellol), and levomenthol

The lozenges are packed in polyvinylchloride-polyvinyl dichloride/aluminium (PVC-PVdC/Alu) blisters packs.

II.2 Drug Substance

The active substance is flurbiprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. Flurbiprofen is practically insoluble in water, freely soluble in ethanol (96%) and methylene chloride. It dissolves in aqueous solutions of alkali hydroxides and carbonates.

Because the active substance is completely dissolved during the manufacturing of the drug product polymorphism is not relevant.

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., the CEP and additional requirements for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The choices of packaging, formulation and manufacturing process are justified in relation to the innovator. The proposed dissolution method is acceptable. The MAH has demonstrated that the test and reference product of the sugar-free orange lozenges is similar at the pH of the saliva.

Manufacturing process
The narrative of the manufacturing has been adequately described. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three commercial batches in accordance with the relevant European guidelines

Control of excipients
The excipients comply with Ph.Eur. requirements, except for the colouring agents and the orange flavour (in-house). These specifications are acceptable.

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 includes tests for description, identification of the drug substance, identification of the colouring agents, average weight, uniformity of content, assay of the drug substance, related substances, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. A risk evaluation on elemental impurities in the drug product and their control have been submitted.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial 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 commercial batches stored at 25°C/ 60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable ICH guidelines demonstrating the stability of the product for 24 months. The MAH did not present the results of appearance for the photostability study. In the absence of this data and as precautionary measure, the MAH included the claim “Store in the original package to protect from light”. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are “Store in the original package in order to protect from light”.

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 Flurbiprofen 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:

- The applicant commits to submit an updated report including the appearance in the photostability study report three months after end of procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Flurbiprofen is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Strepfen Citroen & Honing which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the four studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted four pharmacokinetic studies (see table 1). In study 1 the pharmacokinetic profile of the test product Flurbiprofen lozenges sugar free orange flavour (Geiserpharma S.L., Spain) was compared with the pharmacokinetic profile of the reference product Strepfen sugar-free orange lozenges (Reckitt Benckiser Healthcare B.V., Netherlands). In studies 2, 3 and 4, the pharmacokinetic profile of the test product. Flurbiprofen Geiser Pharma lozenges (Geiserpharma S.L., Spain) was compared with the pharmacokinetic profile of the reference product Strepfen honey & lemon lozenges (Reckitt Benckiser Healthcare B.V., Netherlands).

Table 1. *In vivo* pharmacokinetic studies submitted by MAH comparing test and reference products

Study number	Type of study	Test product	Reference product
1	Pivotal local availability study	sugar-free orange lozenges	Strepfen sugar-free orange lozenges
2	local availability study	sugar mint lozenges	Strepfen honey & lemon

			lozenges
3	local availability study	sugar mint lozenges	Strepfen honey & lemon lozenges
4	systemic bioavailability study	sugar mint lozenges	Strepfen honey & lemon lozenges

The choice of the reference product in the study (study 1) has been justified by comparison of dissolution study results and composition (in simulated saliva pH = 6.2). The formula and preparation of the batch was identical to the formula proposed for marketing.

Pharmacokinetic studies

Pivotal study 1: local availability with Flurbiprofen reference Strepfen sugar-free orange lozenges and test sugar-free orange lozenges

Design

A multiple-dose, randomised, two-treatment, two-sequence, crossover, open-label, controlled and randomised study was carried out under fasted conditions in 48 healthy male (22) and female (26) subjects, aged 18-25 years. Each subject received a single dose (8.75 mg) of one of the two flurbiprofen formulations daily for six days in each treatment period. The lozenge was orally administered with 20 mL water after an overnight fast of at least ten hours, and after rinsing out the mouth. During administration the lozenge was kept in the mouth during different time intervals each day of the week as determined by the randomisation sequence (i.e., 3, 6, 9, 12, 15 or 20 minutes). There were five dosing periods in each treatment period, which were separated by a washout period of 12 hours. There were two treatment periods, which were separated by a washout period of 12 days.

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

48 subjects enrolled in the study. Three subjects were withdrawn from the study. 45 subjects were eligible for pharmacokinetic analysis. The bootstrapping results show a 5% percentile ≥50.

Table 2. Percentage of flurbiprofen released in the different times of consumption (Mean ± SD; CV) with each of the formulations.

Treatment N=45	**Reference**			**Test**		
Time (minutes)	**Mean (%)**	**SD**	**CV (%)**	**Mean (%)**	**SD**	**CV (%)**
3	22.28	15.33	68.83	22.74	13.14	57.80
6	37.33	20.53	55.00	35.20	19.81	56.26
9	49.48	26.31	53.17	48.93	25.40	51.91
12	58.18	27.78	47.75	58.92	26.96	45.77

15	66.88	29.31	43.83	70.57	26.59	37.68
20	76.68	25.60	33.39	77.91	27.07	34.75

Study 2: local availability study with test sugar mint lozenges and reference Strepfen honey & lemon lozenges

Design

A multiple-dose, randomised, two-treatment, two-sequence, crossover, open-label, controlled and randomised study was carried out under fasted conditions in 36 healthy (13 male and 23 female subjects), aged 18-32 years. Each subject received a single dose (8.75 mg, one lozenge) of one of the two flurbiprofen formulations for five days in each treatment period. The lozenge was orally administered with 20 mL water after an overnight fast of at least ten hours, and after rinsing out the mouth. Each one of them would maintain the lozenge in the mouth during a period of time determined by the randomisation sequence: 3 – 6 – 9 – 12 or 15 minutes. There were five dosing periods in each treatment period, which were separated by a washout period of 12 hours. There were two treatment periods, which were separated by a washout period of 12 days.

The percentage of consumed flurbiprofen and therefore the percentage of flurbiprofen released from each formulation at each period of time was calculated using the data of the residual quantity of flurbiprofen in the unconsumed lozenges and the consumption times. The similarity factor (f2-test) was used to compare the dissolution profiles of the test and the reference product.

The design of the study is acceptable.

Results

36 subjects enrolled in the study. One subject was withdrawing during period I due to AE (gastrointestinal). 35 subjects were eligible for pharmacokinetic analysis. Given the RSD (relative standard deviation) values, bootstrapping was performed. The results of the bootstrapping show a 5% percentile ≥50.

Table 3. Percentage of flurbiprofen dissolved or released at each time point, together with the corresponding SD and CV values, for both formulations.

Treatment N=35	**Reference**			**Test**		
Time (minutes)	**Mean (%)**	**SD**	**CV (%)**	**Mean (%)**	**SD**	**CV (%)**
3	43.28	20.58	47.55	44.61	19.78	44.34
6	58.33	18.51	31.73	56.95	19.42	34.10
9	68.49	20.57	30.03	69.79	19.25	27.58
12	76.40	22.26	29.14	77.48	18.41	23.76

15	85.65	15.46	18.05	82.15	17.27	21.02

Study 3: local availability study with test sugar mint lozenges and reference Strepfen honey & lemon lozenges

Design

A multiple-dose, randomised, two-treatment, two-sequence, crossover, open-label, controlled and randomised study was carried out under fasted conditions in 40 healthy (18 male and 22 female subjects), aged 18-27 years. Each subject received a single dose (8.75 mg, one lozenge) of one of the two flurbiprofen formulations for five days in each treatment period. The lozenge was orally administered with 20 mL water after an overnight fast of at least 10 hours, and after rinsing out the mouth. Each one of them would maintain the lozenge in the mouth during a period of time determined by the randomisation sequence: 3 – 6 – 9 – 12 – 14 or 16 minutes. There were five dosing periods in each treatment period, which were separated by a washout period of 12 hours. There were two treatment periods, which were separated by a washout period of 12 days.

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

40 subjects enrolled in the study. 40 subjects were eligible for pharmacokinetic analysis. Given the RSD values, bootstrapping was performed. The results of the bootstrapping show a 5% percentile ≥50.

Table 4. Percentage of flurbiprofen released in the different times of consumption (Mean ± SD; CV) with each of the formulations

Treatment N=40	**Reference**			**Test**		
Time (minutes)	**Mean (%)**	**SD**	**CV (%)**	**Mean (%)**	**SD**	**CV (%)**
3	39.17	12.91	32.97	36.50	12.31	33.71
6	61.74	17.85	28.91	57.27	19.12	33.39
9	74.91	17.68	23.60	72.75	20.01	27.51
12	84.35	18.44	21.86	87.69	16.22	18.49
14	91.46	14.04	15.35	91.43	14.68	16.06
16	92.64	12.51	13.50	94.92	9.84	10.37

Study 4: systemic bioavailability study with test sugar mint lozenges and reference Strepfen honey & lemon lozenges

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, controlled comparative study was carried out under fasted conditions in 18 healthy male (8) and female (10) subjects, aged 18-25 years. Each subject received a single dose (17.5 mg, two lozenges) of one of the two flurbiprofen formulations. A dose of 17.5 mg was chosen for being a common dose used in clinical practice and because it was enough for the correct quantitation of the enantiomers. The lozenge was orally administered after an overnight fast of at least ten hours, and after rinsing the mouth. During administration, the lozenge is kept in the mouth, sucking until its consumption, which should last less than 15 minutes. After 15 minutes, around 160 mL of water was administered to help swallowing the remaining lozenge. There were two dosing periods, separated by a washout period of three days.

Blood samples were collected at 0, 5, 15, 20, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours 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.

S-flurbiprofen and B-flurbiprofen were both measured. The results of S-flurbiprofen will be considered for further discussion as this enantiomer performs as a non-steroidal anti-inflammatory drug.

Results

18 subjects enrolled in the study. 18 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-flurbiprofen 17.5 mg under fasted conditions.

Treatment N=18	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	8001.29 ± 1438.04	8468.89 ± 1593.01	1522.74 ± 356.53	1.00 (0.67 – 3.00)
Reference	8308.86 ± 1737.62	8797.37 ± 1909.09	1645.97 ± 284.73	1.00 (0.50 – 1.50)
***Ratio (90% CI)**	0.97 (0.94 – 1.00)	0.97 (0.94 – 1.00)	0.91 (0.82 – 1.02)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on local availability studies 1, 2 and 3 and systemic bioavailability study 4:
Based on the results of the pivotal local availability study 1, it can be concluded that flurbiprofen 8.75 mg sugar free orange flavour lozenges (the proposed product), and Strepfen® sugar free orange flavour lozenges (reference product) have a comparable *in vivo* release. Furthermore, based on the local availability studies 1 and 2, and the systemic bioavailability study 4, the flurbiprofen 8.75 mg sugar mint flavour lozenges (product not proposed in the current application) are considered therapeutically equivalent to Strepfen® sugar honey & lemon flavour lozenges (8.75 mg). Subsequently, Strepfen sugar-free orange lozenges is considered relevant for showing therapeutic equivalence of the proposed product to the reference product, i.e., Strepfen honey & lemon lozenges. It is therefore acceptable to use Strepfen sugar-free orange lozenges as comparator in the local availability study, and to compare the proposed product to Strepfen sugar-free orange lozenges regarding the systemic bioavailability.

No safety concerns are raised regarding the test product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2, 30 August 2024), 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 Flurbiprofen.

Table 6. 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 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 and experience with the innovator product Strepfen. The MAH demonstrated through one bioequivalence study and three local availability studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the PL has been performed on the basis of a bridging report making reference to Verofen, Flurbigen and Sereno 8.75 mg Lozenges, ES/H/0365,0369,0371/001/DC. 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

Flurbiprofen Healthypharm 8.75 mg lozenges sugar-free (orange) have a proven chemical-pharmaceutical quality and are hybrid forms of Strepfen Citroen & Honing 8,75 mg. Strepfen is a well-known medicinal product with an established favourable efficacy and safety profile.

Taking into account the comparable *in vivo* release of flurbiprofen (based on the results of pivotal study 1) together with the similar composition of the test sugar-free orange lozenges and Strepfen sugar-free orange lozenges, the RMS concludes that the proposed product Flurbiprofen Healthypharm 8.75 mg lozenges sugar-free orange and Strepfen sugar-free orange lozenges have an equivalent local availability.

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 Flurbiprofen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 August 2025.

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
N.A	N.A	N.A	N.A	N.A	N.A