Public Assessment Report
Scientific discussion

Verofen 8.75 mg Lozenges
Flurbigen 8.75 mg Lozenges
Sereno 8.75 mg Lozenges

Flurbiprofen

ES/H/0365, 369 & 371/001/DC

Applicant: Geiserpharma, S.L.

This module reflects the scientific discussion for the approval of **Verofen 8.75 mg lozenges, Flurbigen 8.75 mg Lozenges and Sereno 8.75 mg Lozenges**. The procedure was finalised on January 2017. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

This decentralised application concerns a hybrid version of flurbiprofen, under Verofen 8.75 mg Lozenges, Flurbigen 8.75 mg Lozenges and Sereno 8.75 mg Lozenges trade names.

The legal basis for this application is article 10.3 of Directive 2001/83/EC (hybrid application). The originator product is Strepflam 8.75 Lozenges by Crookes Healthcare/Reckitt Benckiser Healthcare, registered since June 06th, 2001.

With Spain as the Reference Member State in this Decentralized Procedure, Geiserpharma, S.L. is applying for the Marketing Authorisations for Flurbiprofen 8.75 mg Lozenges in:
- − ES/H/0365/001/DC: IT, PL, PT and RO
- − ES/H/0369/001/DC: CZ and SK
- − ES/H/0371/001/DC: BE, DE, IT, LU, NL and PL

Flurbiprofen 8.75 mg Lozenges is indicated for the short term symptomatic relief of sore throat.

The recommended dose for adults and children over the age of 12 years is one lozenge sucked/dissolved slowly in the mouth every 3-6 hours as required. Maximum 5 lozenges in a 24 hour period. It is recommended that this product should be used for a maximum of three days.

This product is not indicated for children under 12 years.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Verofen 8.75 mg Lozenges, Flurbigen 8.75 mg Lozenges and Sereno 8.75 mg Lozenges.

I.   SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

ACTIVE SUBSTANCE
Flurbiprofen is a known active substance described in Ph. Eur. A Ph. Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient.
 The CEP includes re-test period.

FINISHED PRODUCT

Description of the product
Flurbiprofen 8.75mg mint flavour lozenges is provided as clear to yellowish round lozenges mint flavoured.
The qualitative composition is as follows:
- Flurbiprofen
- Sucrose
- Glucose liquid
- Polyethylene glycol 300
- Peppermint oil
- Levomenthol

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

Pharmaceutical development

The pharmaceutical development has been adequately described.

The company has identified the physico-chemical properties of the active substance that are relevant for the product performance. The function and compatibility of the excipients have been adequately discussed.

An *in vitro* release test has been developed. The data provided support its use and the release specification.

Manufacture of the product and process controls

The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.

The commercial batch size is defined.

The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients

The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph.

Product specification

The finished product specification is acceptable. All the analytical methods are sufficiently described. Validation data of methods according to ICH requirements have been submitted.

Container closure system

The proposed packaging material is commonly used in pharmaceutical industry. The certificates of compliance for the packaging materials with European legislation on plastic materials and articles intended to come into contact with food have been provided.

Stability of the product

The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

II-2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Flurbiprofen are well known. As Flurbiprofen is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate

Environmental Risk Assessment (ERA)

The Applicant has submitted ERA data of flurbiprofen. In this regard, logKow value (logKow≈4) was experimentally calculated. In the case of PEC value, it was above the threshold value established in the ERA guideline (EMEA/CHMP/SWP/4447/00). Therefore, the Applicant presented the values for PEC/PNEC ratio, which resulted in a value below the threshold value. The Applicant considered that no Phase II would be necessary.

The conclusions are considered acceptable.

II.3 Clinical aspects

Introduction

To support the application, the Applicant has submitted the following studies:

- A Phase I, randomised, open-label, single-dose, two-sequence, two-period, crossover study to assess the comparative bioavailability of two formulations of Flurbiprofen 8.75 mg in healthy volunteers under fasting conditions.
- An open-label, randomised, multiple-dose, two-sequence, two-treatment crossover local availability study comparing the release at the site of action of two formulations of Flurbiprofen 8.75 mg lozenges administered to healthy volunteers under fasting conditions.
- Phase I clinical trial, randomized, open label, multiple-dose, two treatment, two sequence, cross-over study to assess the comparative bioavailability of two formulations containing 8.75 mg of flurbiprofen administered to healthy volunteers, under fasting conditions.

Because the efficacy of flurbiprofen lozenges is due to local effects of the drug, not only a bioequivalence study (according to the Guideline on the investigation of bioequivalence for immediate release products with systemic action CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) for systemic safety assessment, but also a local availability study as a surrogate of efficacy (according to the Note For Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents, CPMP/EWP/239/95) have been conducted.

Biowaiver

Not applicable as the 8.75 lozenges are tested in vivo.

Bioequivalence

Bioequivalence Study No. G-13-01 (CUNFI-1310) EudraCT number: 2013-004110-18

This was a Phase I, randomised, open-label, single-dose, two-sequence, two-period, crossover study to assess the comparative bioavailability of two formulations of Flurbiprofen 8.75 mg in healthy volunteers under fasting conditions.

The Clinical part of the study was performed from November 06th, 2014 to December 01st, 2014 at Clinical Research Unit. Department of Clinical Pharmacology of the Clínica Universidad de Navarra (CUN) 31008 Pamplona (Spain).

The analytical part was conducted at Laboratorio Kymos Pharma Services, S.L., Parc Científic de Barcelona, Baldiri Reixac, 10, 08028 Barcelona (Spain) from December 01st, 2014 to December 17th, 2014.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

This was a randomised, open-label, single-dose, two-sequence, two-period, crossover study to assess the comparative bioavailability of two formulations of Flurbiprofen 8.75 mg in healthy volunteers under fasting conditions with a washout of a minimum of 3 days.

A single dose bioequivalence study in fasting state for the comparison of the systemic safety profile is acceptable as the application concerns an oral immediate release formulation (lozenges). In addition, the administration of the reference product is irrespective of food intake. The wash-out period of a minimum of 3 days (more than five times the half-lives) is considered adequate since the drug has a half-life of approximately 3-6 hours and no pre-dose level was detected.

Considering the expected time to peak concentration (30-40 minutes) and the elimination half-life, the sampling schedule and the sampling time period of 24 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent over the first 1 hour and should be sufficient to allow an accurate measurement of C_{max} and t_{max}.

<u>Test product</u>: Flurbiprofen 8.75 mg lozenges manufactured Pierre Fabre Medicaments Production Laboratories. Batch number: A99001. Batch size: 26,400 lozenges. Proposed batch size: 26,400 lozenges. Expiry date: May 2016. Assay (content): 101.18% of label claim.

<u>Reference product</u>: Strepfen 8.75 mg lozenges manufactured by Reckitt Benckiser Healthcare International Limited from the Portuguese market. Batch number: AX764. Expiry date: November 2016. Assay (content): 98.20 % of label claim.

Flurbiprofen was administered orally, as lozenges for sucking. Before administration of the medication the volunteer washed his/her mouth out with 20 ml of water.

The reference product is adequate with regards to expiry date, content and it was obtained from the Portuguese market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

The dose of flurbiprofen administered to the healthy volunteers was of 17.5 mg in each of the treatment periods. This dose is considered acceptable because it was necessary to measure with adequate precision and accuracy both enantiomers. This higher dose is known to be safe for the healthy volunteers and the drug pharmacokinetics is linear.

A total of 18 healthy volunteers of both sexes were enrolled in the clinical trial. All of them completed the study according to the protocol.

There were some deviations in the times of blood sample extractions. All delays were taken into account when performing the pharmacokinetic analysis of the data.

No other protocol deviations occurred prior to or during the study period.

No concomitant medication was administered during the study.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

The selected primary pharmacokinetics C_{max} and AUC_{0-t} variables are appropriate for a single dose bioequivalence study of an IR product.

The evaluation of bioequivalence was based upon measured concentrations of both enantiomers.

Statistical analysis

The evaluation of the bioequivalence hypothesis was based on the AUC_{0-t} and C_{max} obtained for the two formulations. The C_{max} and AUC_{0-t} parameters of flurbiprofen enantiomers were subjected to log transformation for the bioequivalence analysis. Comparative bioavailability was assessed using parametric confidence intervals (90%); residual variance used in the calculation was obtained from the ANOVA with sequence, period, subject (sequence) and formulations as fixed factors. For decision-making, an acceptance range of 20% was applied.

Results

The 90% confidence intervals of the mean treatment T/R ratios are shown in the following tables:

Bioequivalence evaluation of S-flurbiprofen

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC$_{0-t}$)	91.69	81.96-101.74
Ln (C$_{max}$)	96.79	93.86-99.80

Bioequivalence evaluation of R-flurbiprofen

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC$_{0-t}$)	99.07	95.44-102.84
Ln (C$_{max}$)	91.41	81.61-102.39

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product with respect to the extent and rate of absorption/exposure as the 90.00% confidence intervals for the ln-transformed AUC$_{0-t}$ and C$_{max}$ are within the acceptance range of 80-125%.

Local availability Study No. G 13-01-1 (CUNFI-1405) EudraCT Number: 2014-001880-11

This was an open-label, randomised, multiple-dose, two-sequence, two-treatment crossover local availability study comparing the release at the site of action of two formulations of Flurbiprofen 8.75 mg lozenges administered to healthy volunteers under fasting conditions.

The Clinical part of the study was performed from April 13th, 2015 to May 15th, 2015 at Clinical Research Unit. Department of Clinical Pharmacology of the Clínica Universidad de Navarra (CUN) 31008 Pamplona (Spain).

The analytical portion was conducted at Laboratorio Kymos Pharma Services, S.L., Parc Científic de Barcelona, Baldiri Reixac, 10, 08028 Barcelona (Spain) from May 14th, 2015 to May 25th, 2015.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analyticaland the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

This was Phase I, multiple-dose, open-label, 2x2 crossover, controlled and randomised clinical trial. Each subject received one lozenge taken daily for five days in each treatment period. The resulting sequences, TR and RT, were randomised. The medication was administered under fasting conditions.

The study was designed to determine the amount of active ingredient remaining in the lozenge at specific time intervals after its consumption.

A minimum washout period of 12 hours was established.

Lozenges were administered orally, after rinsing out the mouth and ingesting 20 ml of water. The medication was placed in the mouth of the volunteer, asking the subject to maintain it in the mouth without swallowing or chewing it.

The percentage of the active substance released or dissolved from each lozenge at each sampling time (3, 6, 9, 12 or 15 minutes) was calculated using the amount remaining in each lozenge at each of the corresponding consumption times, using the following formula:

$$Q_t\ (\%) = \frac{Q_{100} - Q_{0-t}}{Q_{100}} \cdot 100$$

Where Q_t is the percentage dissolved at a given time of consumption (t), Q_{100} corresponds to the initial amount of active substance in each of the lozenges (8.75 mg) and Q_{0-t} is the amount of flurbiprofen in the remaining lozenge at time (t).

Remnant of the lozenges at each sampling time were diluted in a matrix of established volume in which the concentration of flurbiprofen was measured, thus allowing calculation of Q_{0-t}.

The study design is considered acceptable to calculate the percentage of the active substance released or dissolved in vivo from each lozenge at each sampling time (3, 6, 9, 12 or 15 minutes) based on the amount of active ingredient remaining in the lozenge under the assumption that the low amount of the drug that is released from the lozenge is dissolved immediately in saliva.

The wash-out period of a minimum of 12 hours is considered adequate to ensure that the baseline saliva conditions were the same.

Test product: Flurbiprofen 8.75 mg lozenges manufactured Pierre Fabre Medicaments Production Laboratories. Batch number: A99001. Expiry date: May 2016. Assay (content): 101.18% of label claim.

Reference product: Strepfen 8.75 mg lozenges manufactured by Reckitt Benckiser Healthcare International Limited from the Portuguese market. Batch number: BJ013. Expiry date: December 2017. Assay (content): 98.58 % of label claim.

The reference product is adequate with regards to expiry date, content and it was obtained from the European Union market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

Thirty-six volunteers were included in the study (13 males and 23 females). Thirty-five of them completed the study. One volunteer was withdrawn from the study during period 1 due to the appearance of adverse events (stomachache and diarrhoea).

The subjects are considered acceptable with regards to demographic characteristics.

The inclusion and exclusion criteria are considered to be acceptable.

No relevant protocol deviations occurred prior to or during the study period.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the samples.

Statistical analysis

As primary parameter, the similarity factor f_2 for flurbiprofen was calculated after the administration of both formulations. Both profiles were considered similar if the factor was higher than 50.

Since the calculation of f_2 cannot be used to compare the dissolution profiles when the %CV is more than 20% for the first point or more than 10% from second to last time point. Therefore, a "Model-Independent Multivariate Confidence Region Procedure" (Mahalanobis distance) was proposed as an alternative methodology to handle this issue in case high within-batch variability is observed.

The Mahalanobis distance method was performed using the dissolution profile comparison software DDsolver, which is an add-in program for Microsoft Excel (Zhang et al., 2010). Microsoft Excel 2003 or above will be used within the analyses.

According to this approach, for two profiles to be considered similar, the difference between the test and reference profiles should be less than or equal to the maximum expected difference between any two batches of approved products (also called the similarity limit or tolerance limit). Due to the type of study (in vivo release rather than a conventional in vitro dissolution), the nature of the formulations (intended to be slowly dissolved in the oral cavity) and the expected high variability, the tolerance limit to consider similarity between products was established at 20%.

Results

The value of f_2 obtained was of 83.05. As a result of the variance observed at different points, the Mahalanobis distance was calculated, as an alternative model independent method.
Table below shows the comparison between both products.

Mahalanobis Distance (D_M): Estimate [90%CI]	Tolerance limit (D_g)	Critical value (D_{M_max})	$D_{M, upper\_90} < D_{M\_max}$	Similarity
0.41 [-0.36 to 1.18]	20%	1.34	Yes	Yes

The results of the Mahalanobis distance approach indicate that the upper bounds of the 90% confidence limits ($D_{M, upper\_90}$) between both test and reference formulations were inferior to the maximum critical value (D_{M_max}) corresponding to the 20% tolerance limit in the evaluable population.
A new analysis of Mahalanobis distance using a 15% tolerance limit was submitted. The results below approach indicate that the upper bounds of the 90% confidence limits (DM, upper_90) between both test and reference formulations were superior to the maximum critical value (D_{M_max}) corresponding to the 15% tolerance limit in the evaluable population (n=35).

This fails to show similarity between flurbiprofen 8.75 mg GeiserPharma Lozenges (TEST) and Strepfen 8.75 mg lozenges (REFERENCE), with respect to local availability of flurbiprofen.

Mahalanobis Distance (D_M): Estimate [90%CI]	*Tolerance limit (D_g)*	*Critical value (D_{M_max})*	*$D_{M, upper\_90} < D_{M\_max}$*	*Similarity*
0.41 [-0.36 to 1.18]	*15%*	*1.01*	*No*	*No*

In addition, the Applicant has performed an alternative statistical methodology; a population approach analysis, before application of Mahalanobis distance. Direct application of the Mahalanobis distance approach to the observations from study 1405, even if setting the tolerance limit to a maximum of 20% in compensation for the fact that this was not a conventional in vitro dissolution test, may have not been entirely appropriate if taken into consideration the special design features. The unavoidable fact that each sample was taken from a different lozenge unit introduced considerable bias or "noise" into the observations, which explains the occurrence of outlying or illogical profiles (i.e., extent of dissolution not consistent with sucking time).

This time, the results of the Mahalanobis distance approach based on individual predictions indicated that the upper bounds of the 90% confidence limits ($D_{M, upper\_90}$) between both test and reference formulations were inferior to the maximum the below table).

Mahalanobis Distance (D_M): Estimate [90%CI]	Tolerance limit (D_g)	Critical value (D_{M_max})	$D_{M, upper\_90} < D_{M\_max}$	Similarity
0.65 [-0.12 to 1.42]	10%	48.13	Yes	Yes

This allowed the Applicant to conclude that both formulations, Flurbiprofen 8.75 mg Lozenges (Test) and Strepfen 8.75 mg lozenges (Reference), behave similarly with respect to the local availability of flurbiprofen when the aforementioned "noise" is eliminated or minimized and unbiased individual predictions are provided through a suitable population model within a mixed effects framework.

However, the Multivariate Statistical Distance (MSD) or Mahalanobis Distance is not considered as a valid methodoly for the comparison for dissolution profiles because the limitations of this methodology as described in the scientific literature (Mangas-Sanjuan V, Colon-Useche S, Gonzalez-Alvarez I, Bermejo M, Garcia-Arieta A. Assessment of the Regulatory Methods for the Comparison of Highly Variable Dissolution Profiles. AAPS J. 2016 Nov;18(6):1550-1561). Furthermore, the two acceptance ranges defined by the sponsor do not correspond to a 10% difference in the amount dissolved, which is the acceptance range to be used according to the Guideline on the investigation of bioequivalence. Similarly, the population approach was not considered an acceptable methdology to compare in vivo dissolution profiles.

Complementarily and as supportive of the similarity of the dissolution profiles as well, the dissolution profiles of test and reference formulations obtained from the *in vivo* release study (1405) were compared by applying a f_2-bootstrap methodology. The similarity factor is estimated for each bootstrap dataset and 90% confidence intervals of f_2 are obtained. Similarity between two dissolution profiles is established when the lower limit of the 90% CI of f_2 value is equal or greater than 50.

The different analysis of f_2-bootstrap reported here include the simulation of 5000 bootstrap and the 90% CI of f_2 was estimated in the results included in this report. The number of sampling times considered in the estimation of similarity factor followed the FDA (sampling times until both test and reference products have reached >85% dissolved) and EMA (sampling times up to when >85% is achieved by one of the products, either test or reference) requirements.

The results obtained show that, according to the requirements of data points selection of EMA or FDA, both formulations (Reference and Test) are similar because the lower limit of the 90% CI is higher than 50, as reflected in the table below:

Study	Criteria	Mean f2	Variance f2	IC90% (n=5000)
1405	EMA	59.1	17.5	[51.3-64.8]
	FDA	59.1	17.2	[50.8-64.6]

In conclusion, the results of the f_2-bootstrap methodology indicate that both formulations of flurbiprofen (Strepfen® (Reference)-Flurbiprofen Geiser Pharma (Test) administered in 35 healthy volunteers first (Study 1405) are similar. According to the EMA and FDA requirements, the lower limit of the 90% confidence interval estimated using f_2-bootstrap methodology is higher than the established limit (50) to conclude similarity between two formulations (51.3-50.8).

Local availability Study Code G13-01-2 (CUNFI-1606); EudraCT Number: 2016-000846-68

Phase I, randomized, open label, multiple-dose, two treatment, two sequence, cross-over clinical trial to assess the comparative bioavailability of two formulations containing 8.75 mg of flurbiprofen administered to healthy volunteers, under fasting conditions

The Clinical part of the study was performed at Clinical Research Unit. Department of Clinical Pharmacology of the Clínica Universidad de Navarra (CUN) 31008 Pamplona (Spain) from May 05th, 2016 to June 13th, 2016.

The analytical part was conducted at Laboratorio Kymos Pharma Services, S.L., Parc Científic de Barcelona, Baldiri Reixac, 10, 08028 Barcelona (Spain) from June 23rd, 2016 to July 01st, 2016.

Design

Phase I, randomized, open label, multiple-dose, two treatment, two sequence, cross-over clinical trial to assess the comparative bioavailability of two formulations containing 8.75 mg of flurbiprofen administered to healthy volunteers, under fasting conditions. Each subject received six doses of the test formulation (T) and six doses of the reference formulation (R) per period to calculate the amount dissolved at each of the six sampling times. The resulting sequences, TR and RT, were randomised.

The study was designed to determine the amount of active ingredient remaining in the lozenge at specific time intervals after its consumption.

A minimum washout period of 12 hours was established.

Lozenges were administered orally, after rinsing out the mouth and ingesting 20 ml of water.

The percentage of the active substance released or dissolved from each lozenge at each sampling time (3, 6, 9, 12, 14 or 16 minutes) was calculated using the amount remaining in each lozenge at each of the corresponding consumption times, using the following formula:

$$Q_t\ (\%) = \frac{Q_{100} - Q_{0-t}}{Q_{100}} \cdot 100$$

Where Q_t is the percentage dissolved at a given time of consumption (t), Q_{100} corresponds to the initial amount of active substance in each of the lozenges (8.75 mg) and Q_{0-t} is the amount of flurbiprofen in the remaining lozenge at time (t).

Remnant of the lozenges at each sampling time was diluted in a matrix of established volume in which the concentration of flurbiprofen was measured, thus allowing calculation of Q_{0-t}.

Test product: Flurbiprofen 8.75 mg lozenges manufactured Pierre Fabre Medicaments Production Laboratories. Batch number: A99002. Expiry date: July 2016. Assay (content): 96.73% of label claim.

Reference product: Strepfen 8.75 mg lozenges manufactured by Reckitt Benckiser Healthcare International Limited from the Portuguese market. Batch number: BW932. Expiry date: February 2016 Assay (content): 96.73 % of label claim.

The test and reference product are adequate for a hybrid application. Reference product was obtained from the European market.

Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

Forty volunteers were included in the study (18 males and 22 females). All of them completed the study.

No relevant protocol deviations occurred prior to or during the study period.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the samples.

Statistical analysis

Evaluation criteria (relative bioavailability):

1. Primary parameter: similarity factor (f_2), whenever the dissolution profiles of the test and reference formulations fit the conditions to allow this calculation.

2. Secondary parameter: Model-independent Multivariate Confidence Region Procedure (Mahalanobis distance method).

Calculation of the similarity factor f_2 to establish the similarity between both formulations is not considered correct because of the high variability of the data.

As the calculation of the similarity factor f_2 cannot be used to compare the dissolution profiles when the %CV is more than 20% for the first point or more than 10% from second to last time point, a "Model-Independent Multivariate Confidence Region Procedure" (Mahalanobis distance) was used based on the methodology described in the FDA guideline on dissolution.

Results

As a result of the variance observed at different points, and just as it had been set out in the protocol and in the statistical analysis plan, the Mahalanobis distance was calculated, as an alternative model independent method. The results are shown in the following table.

Table below shows the comparison between both products

Population	Substance	Mahalanobis distance: midpoint [CI 90%]	Significance limit: 15% of distance	Conclusión
(n=40)	flurbiprofen	0.65 [-0.11 to 1.43]	1.73	Distance < 15 %

Population	Substance	Mahalanobis distance: midpoint [CI 90%]	Significance limit: 10% of distance	Conclusión
(n=40)	flurbiprofen	0.65 [-0.11 to 1.43]	1.15	Distance > 10 %

The results of the Mahalanobis distance approach indicate that the upper bounds of the 90% confidence limits ($D_{M, upper\_90}$) between both test and reference formulations in the evaluable population (n=40) were inferior to the maximum critical value (D_{M_max}) corresponding to the 15% tolerance limit established in the SAP. This allows concluding that the two study formulations, flurbiprofen 8.75 mg GeiserPharma Lozenges (TEST) and Strepfen 8.75 mg lozenges (REFERENCE), behave similarly with respect to local availability of flurbiprofen.

Even if similarity could not be proven when considering a tolerance limit of 10%, such a tight limit does not seem to be appropriate herein in view of the high variability characterizing the performance of lozenge formulations in the experimental setting.

Again, the Multivariate Statistical Distance (MSD) or Mahalanobis Distance was not considered as a valid methodoly for the comparison for dissolution profiles because the limitations of this methodology as described in the scientific literature (Mangas-Sanjuan V, Colon-Useche S, Gonzalez-Alvarez I, Bermejo M, García-Arieta A. Assessment of the Regulatory Methods for the Comparison of Highly Variable Dissolution Profiles. AAPS J. 2016 Nov;18(6):1550-1561). Furthermore, the acceptance ranges defined by the sponsor as a tolerance limit of 15% or 20% do not correspond to a 10% difference in the amount dissolved, which is the acceptance range to be used according to the Guideline on the investigation of bioequivalence. Therefore, the study results were assessed based on the 90% confidence interval of the f_2 similarity factor. Similarity was concluded as the whole 90% confidence interval was above 50 (see the table below).

Study	Criteria	Mean f2	Variance f2	IC90% (n=5000)
1606	EMA	61.0	20.1	[52.3-67.5]
	FDA	61.6	19.7	[53.6-67.8]

According to the EMA and FDA requirements, the lower limit of the 90% confidence interval estimated using f_2-bootstrap methodology is higher than the established limit (50) to conclude similarity between two formulations (52.3-53.6).

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the submitted evidence for Flurbiprofen 8.75 mg lozenges can be considered equivalent to Strepflam 8.75 Lozenges by Crookes Healthcare/Reckitt Benckiser Healthcare.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2017.