Public Assessment Report

Decentralised Procedure

Stafen Direct 8.75mg Oromucosal Spray

Procedure No: UK/H/5072/001/DC

UK Licence No: PL 00063/0715

Reckitt Benckiser Healthcare (UK) Limited
Lay Summary

Strefen Direct 8.75mg Oromucosal Spray
(flurbiprofen)

This is a summary of the public assessment report (PAR) for Strefen Direct 8.75mg Oromucosal Spray (PL 00063/0715; UK/H/5072/001/DC). It explains how Strefen Direct 8.75mg Oromucosal Spray was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Strefen Direct 8.75mg Oromucosal Spray.

For practical information about using Strefen Direct 8.75mg Oromucosal Spray, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Strefen Direct 8.75mg Oromucosal Spray and what is it used for?
Strefen Direct 8.75mg Oromucosal Spray is used for the short-term relief of symptoms of sore throats such as throat soreness, pain, difficulty swallowing and swelling. This medicine is only intended for use in adults aged 18 years and over.

How does Strefen Direct 8.75mg Oromucosal Spray work?
Strefen Direct 8.75mg Oromucosal Spray contains the active substance flurbiprofen. Flurbiprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which work by changing how the body responds to pain, swelling and high temperature.

How is Strefen Direct 8.75mg Oromucosal Spray used?
Strefen Direct 8.75mg Oromucosal Spray should be used for the shortest time necessary to relieve the symptoms. It should not be used in children or adolescents under 18 years.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

One dose of three sprays should be administered to the back of the throat every 3-6 hours as required, up to a maximum of 5 doses in a 24-hour period.

Strefen Direct 8.75mg Oromucosal Spray can only be obtained with a prescription.

What benefits of Strefen Direct 8.75mg Oromucosal Spray have been shown in studies?
The company provided its own data on efficacy and safety studies. These studies have shown that Strefen Direct 8.75mg Oromucosal Spray is effective in treating the symptoms of sore throat.

What are the possible side effects from Strefen Direct 8.75mg Oromucosal Spray?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur with using Strefen Direct 8.75mg Oromucosal Spray, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.
Why is Strefen Direct 8.75mg Oromucosal Spray approved?
It was decided that the benefits of Strefen Direct 8.75mg Oromucosal Spray are greater than the risks, and the grant of the marketing authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Strefen Direct 8.75mg Oromucosal Spray?
A risk management plan has been developed to ensure that Strefen Direct 8.75mg Oromucosal Spray is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Strefen Direct 8.75mg Oromucosal Spray
Austria, Belgium, Bulgaria, Czech Republic, Germany, Spain, France, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia and the UK agreed to grant a marketing authorisation for Strefen Direct 8.75mg Oromucosal Spray on 24 September 2014. The marketing authorisation in the UK was granted on 09 October 2014.

The full PAR for Strefen Direct 8.75mg Oromucosal Spray follows this summary.

For more information about treatment with Strefen Direct 8.75mg Oromucosal Spray, read the PIL or contact your doctor or pharmacist.

This summary was last updated in December 2014.
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I  Introduction
Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to Reckitt Benckiser Healthcare (UK) Limited for the medicinal product Strefen Direct 8.75mg Oromucosal Spray. This product is a prescription-only medicine (POM) indicated for the short-term symptomatic relief of acute sore throat in adults.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Bulgaria, Czech Republic, Germany, France, Spain, Hungary, Ireland, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia and Italy as Concerned Member States (CMSs). This application was made under Article 8(3) of Directive 2001/83/EC, as amended, for a known active substance.

The medicinal product contains the active substance flurbiprofen.

Flurbiprofen is a propionic acid derivative non-steroidal anti-inflammatory drug (NSAID), which acts through inhibition of prostaglandin synthesis. In humans flurbiprofen has potent analgesic, antipyretic and anti-inflammatory properties and the 8.75 mg dose dissolved in artificial saliva has been shown to reduce prostaglandin synthesis in cultured human respiratory cells. According to studies using the whole blood assay, flurbiprofen is a mixed COX-1/COX-2 inhibitor with some selectivity towards COX 1.

The 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. An overview based on a literature review is, thus, appropriate.

Two bioavailability studies were submitted, comparing different forms of test product (flurbiprofen 8.75mg spray) versus honey and lemon flavour flurbiprofen 8.75mg lozenges. Further to these, a clinical trial was also conducted to demonstrate the efficacy of the test product (flurbiprofen 8.75mg oromucosal spray). The studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For the manufacturing sites outside the Community the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports issued by the inspection services of the MHRA as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfills the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The MA holder has provided a satisfactory Environmental Risk Assessment (ERA).
The RMS and CMSs considered that the application could be approved at the end of procedure (Day 210) on 24 September 2014. After a subsequent national phase, a licence was granted in the UK on 09 October 2014.
II Quality aspects

II.1 Introduction

The product is an oromucosal spray, solution, which is a clear/colourless to slightly yellow solution, with a taste of cherry and mint.

The excipients present are betadex, disodium phosphate dodecahydrate, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium hydroxide, mint flavour (comprising: flavouring substance(s), flavouring preparation(s), propylene glycol E1520, glycercyl triacetate (triacetin) E1518), cherry flavour (comprising: flavouring substance(s), flavouring preparation(s), propylene glycol E1520, water), N,2,3-trimethyl-2-isopropylbutanamide, saccharin sodium, hydroxypropylbetadex and purified water.

The oromucosal spray is presented in a white opaque high-density polyethylene bottle with a multi-component pump unit and protective polypropylene overcap. The pump is comprised of polyoxymethylene, low-density polyethylene, high-density polyethylene, polypropylene, stainless steel and PIB Compound (Polyisobutylene – Rubber). The pack size of the product is 15 ml of oromucosal spray, solution.

II.2 Drug Substance

Flurbiprofen

INN: Flurbiprofen
Chemical Name: (2RS)-2-(2-Fluorobiphenyl-4-yl)propanoic acid
Structure:

```
F       H
\   /   \   /   \   /   \   /
|  |   |  |   |  |   |  |
/  /   /  /   /  /   /  /  /
O -C-C-\_\_/ -C-C-O

and enantiomer
```

Molecular formula: C\textsubscript{15}H\textsubscript{13}FO\textsubscript{2}
Molecular weight: 244.3
Appearance: White or almost-white crystalline powder.
Solubility: Practically insoluble in water, freely soluble in ethanol (96%) and in methylene chloride. It dissolves in aqueous solutions of alkali hydroxides and carbonates.

Flurbiprofen is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, flurbiprofen, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3 Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development was to develop an oromuscosal throat spray to deliver 8.75 mg of flurbiprofen. The development of the formulation has been adequately described.

All the excipients used in the manufacture of the proposed formulation, other than the flavouring agents (N,2,3-trimethyl-2-isopropylbutanamide and the mint and cherry flavouring agent), comply with their respective European Pharmacopoeial monographs. The flavouring agents are controlled in line with suitable in-house specifications and comply with the European Regulation for flavourings (EC 1334/2008).

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contain material of animal or human origin.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with data from three production-scale batches and is satisfactory.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from three production-scale batches and these comply with the release specification. Certificates of analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years (unopened) and 6 months (after first opening), with special storage conditions of “Do not refrigerate or freeze”.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.
III  Non-clinical aspects
The 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. An overview based on a literature review is, thus, appropriate.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.

The applicant submitted an Environmental Risk Assessment (ERA). The predicted environmental concentration of flurbiprofen in the surface water (PECsurfacewater value), 0.2 µg/l, is above the threshold of 0.01 µg/l and, therefore, a Phase II environmental fate and effects assessment was conducted. The data submitted for the Phase II environmental effects assessment for flurbiprofen did not identify any risks for any of the relevant environmental compartments. Therefore, there is no requirement for any specific precautionary or safety measures. No risks were identified for the aquatic compartment, the groundwater compartment, or micro-organisms.

In conclusion, this application is approvable from a non-clinical point of view.

IV  Clinical aspects

IV. 1  Introduction
Two bioavailability studies and a clinical trial were submitted to support this application. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV. 2  Pharmacokinetics
Pilot Bioavailability Study
A pilot bioavailability study was undertaken to compare the bioequivalence of flurbiprofen from four 8.75 mg flurbiprofen sprays (test products B, C, D and E), comprising different flavours and excipients, with that from flurbiprofen 8.75 mg honey and lemon lozenges (reference product A).

An open, randomised, single-dose five-way crossover, comparative, bioavailability, pilot study was undertaken in 12 male and female healthy volunteers, under fasting conditions.

Each subject was dosed with each treatment once according to the randomisation schedule. When receiving the lozenge, subjects were administered one 8.75 mg flurbiprofen lozenge and instructed to suck this until it had dissolved. When receiving the spray, subjects were administered a single dose of 3 sprays (each 180 μL), for a total volume of 540 μL, from a 15 mL spray bottle containing 8.75 mg flurbiprofen/540 μL.

Blood samples were taken pre-dose and up to 720 minutes post-dose. The wash-out period was between 4 and 7 days.

The main pharmacokinetic results are presented below:
Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameter $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$: Treatment B versus Treatment A and Treatment C versus Treatment A

<table>
<thead>
<tr>
<th>Parameters</th>
<th>% Geometric Mean Ratio B versus A</th>
<th>CLS (90% Confidence) B versus A</th>
<th>% Geometric Mean Ratio C versus A</th>
<th>CLS (90% Confidence) C versus A</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>86.59</td>
<td>77.20 – 97.13</td>
<td>87.03</td>
<td>77.59 – 97.62</td>
</tr>
<tr>
<td>$AUC_{0-t}$</td>
<td>85.74</td>
<td>77.37 – 95.02</td>
<td>83.28</td>
<td>75.15 – 92.29</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$</td>
<td>87.06</td>
<td>78.45 – 96.61</td>
<td>83.71</td>
<td>75.43 – 92.89</td>
</tr>
</tbody>
</table>

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each])
Treatment C = 15mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each])

Summary of statistical comparisons of plasma flurbiprofen pharmacokinetic parameter $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$: Treatment D versus Treatment A and Treatment E versus Treatment A

<table>
<thead>
<tr>
<th>Parameters</th>
<th>% Geometric Mean Ratio D versus A</th>
<th>CLS (90% Confidence) D versus A</th>
<th>% Geometric Mean Ratio E versus A</th>
<th>CLS (90% Confidence) E versus A</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>78.35</td>
<td>69.88 – 87.85</td>
<td>81.60</td>
<td>72.78 – 91.49</td>
</tr>
<tr>
<td>$AUC_{0-t}$</td>
<td>77.54</td>
<td>70.00 – 85.90</td>
<td>76.25</td>
<td>68.82 – 84.47</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$</td>
<td>78.71</td>
<td>70.95 – 87.32</td>
<td>77.26</td>
<td>69.65 – 85.71</td>
</tr>
</tbody>
</table>

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment D = 15mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each])
Treatment E = 15mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each])

The 90% confidence intervals (CIs) of the geometric mean ratios for $C_{\text{max}}$ and AUCs of the sprays to the lozenge were outside the 80.00% – 125.00% range. Therefore this study did not show bioequivalence between the spray formulation and the lozenge.

As bioequivalence between the flurbiprofen 8.75 mg sprays and the flurbiprofen 8.75 mg honey and lemon lozenges (reference product A) had not been demonstrated, further work was carried out to determine whether the complete dose of flurbiprofen was being dispensed by the volunteers and nurses at the study centre. It was found that the mean dose being delivered by the volunteers and nurses when using the spray was only 81.55% and 79.67% of the target dose, respectively. It was considered that this under-dosing was likely to have been due to the instructions for product use, which stated that the product should be sprayed three times in quick succession. The wording of these instructions resulted in the user not delivering the full dose, which further investigation showed to be due to the pump not being fully depressed during each spray stroke. In light of this finding, new instructions were written and tested. The results of this test showed that when using the new dosing instructions, the mean proportion of the dose delivered by participants was 95.87%. Therefore these new written dosing instructions were subsequently used for the pivotal pharmacokinetic study.
A pivotal bioavailability study was undertaken to compare the bioequivalence of flurbiprofen from two 8.75 mg flurbiprofen oral sprays (test products B and D), comprising different flavours and excipients, with that from flurbiprofen 8.75 mg honey and lemon lozenges (reference product A). The formulation for test product D was subsequently chosen by the applicant as the finished product formulation for Strefen Direct 8.75 mg Oromucosal Spray.

**An open, randomised, single-dose three-way crossover, comparative, bioavailability, pivotal study was undertaken in 33 healthy male and female volunteers under fasting conditions.**

Each subject was dosed with each treatment once according to the randomisation schedule. When receiving the lozenge, subjects were administered one flurbiprofen 8.75 mg honey and lemon lozenge and instructed to suck this until it had dissolved. When receiving the spray, subjects were administered a single dose of 3 sprays (each 180 μL), for a total volume of 540 μL, from a 15 mL spray bottle containing 8.75 mg flurbiprofen/540 μL.

Blood samples were taken pre-dose and up to 720 minutes post-dose. The wash-out period between treatment dosing was between 4 and 7 days.

The main pharmacokinetic results are presented below:

**Summary of statistical comparisons of plasma flurbiprofen pharmacokinetic parameter AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub>: Treatment B versus Treatment A**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric LS Means</th>
<th>Confidence Intervals</th>
<th>%Geometric Mean Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1561.083</td>
<td>1553.543</td>
<td>95.41 – 105.84</td>
<td>0.8752</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/mL)</td>
<td>5559.887</td>
<td>5693.575</td>
<td>95.44 – 99.92</td>
<td>0.0890</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.hr/mL)</td>
<td>6103.841</td>
<td>6245.435</td>
<td>95.35 – 100.18</td>
<td>0.1258</td>
</tr>
</tbody>
</table>

Treatment A = Flurbiprofen 8.75 mg honey and lemon lozenge
Treatment B = 8.75 mg/540 μL flurbiprofen (3 sprays [180 μL each])

The 90% confidence intervals of the geometric mean ratios for AUC<sub>0-t</sub> and C<sub>max</sub> for treatment B (8.75 mg flurbiprofen oral spray) and the reference product A (flurbiprofen 8.75 mg honey and lemon lozenge) are within the 80.00%-125.00% range. Based on these results, the 8.75 mg/540 μL flurbiprofen Spray B and reference product A (flurbiprofen 8.75 mg honey and lemon lozenge) formulations are bioequivalent under fasting conditions.

**Summary of statistical comparisons of plasma flurbiprofen pharmacokinetic parameter AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub>: Treatment D versus Treatment A**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric LS Means</th>
<th>Confidence Intervals</th>
<th>%Geometric Mean Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1581.294</td>
<td>1552.974</td>
<td>96.61 – 107.32</td>
<td>0.5640</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/mL)</td>
<td>5672.142</td>
<td>5694.360</td>
<td>97.13 – 102.15</td>
<td>0.7941</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.hr/mL)</td>
<td>6232.138</td>
<td>6245.769</td>
<td>96.95 – 102.70</td>
<td>0.8984</td>
</tr>
</tbody>
</table>

Treatment A = Flurbiprofen 8.75 mg honey and lemon lozenge
Treatment D = 8.75 mg/540 μL flurbiprofen (3 sprays [180 μL each])

Geometric LS Means = Geometric least square means.
The 90% confidence intervals of the geometric mean ratios for $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ for treatment D (Strefen Direct 8.75 mg Oromucosal Spray) and the reference product A (flurbiprofen 8.75 mg honey and lemon lozenge) are within the 80.00%-125.00% range. Based on these results, Strefen Direct 8.75 mg Oromucosal Spray and flurbiprofen 8.75 mg honey and lemon lozenge formulations are bioequivalent under fasting conditions.

### Summary of statistical comparisons of plasma flurbiprofen pharmacokinetic parameter $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$, and $C_{\text{max}}$: Treatment D versus Treatment B

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric LS Means</th>
<th>Confidence Intervals</th>
<th>%Geometric Mean Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1582.295</td>
<td>1561.701</td>
<td>96.13 – 106.78</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng·hr/mL)</td>
<td>5668.292</td>
<td>5562.047</td>
<td>98.64 – 105.29</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng·hr/mL)</td>
<td>6228.160</td>
<td>6107.425</td>
<td>98.50 – 105.58</td>
</tr>
</tbody>
</table>

Treatment B = 8.75 mg/540 μL flurbiprofen (3 sprays [180 μL each])
Treatment D = 8.75 mg/540 μL flurbiprofen (3 sprays [180 μL each])

Geometric LS Means = Geometric least square means.

The 90% confidence intervals of the geometric mean ratios for $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ for treatment D (Strefen Direct 8.75 mg Oromucosal Spray) and treatment B (8.75 mg flurbiprofen oral spray) are within the 80.00%-125.00% range. Based on these results, the 8.75 mg/540 μL flurbiprofen Spray B and Strefen Direct 8.75 mg Oromucosal Spray formulations are bioequivalent under fasting conditions.

### IV.3 Pharmacodynamics

Flurbiprofen is a widely used active substance and the pharmacodynamic properties are well known. The applicant has not provided any studies investigating the pharmacodynamics of Strefen Direct 8.75mg Oromucosal Spray and further studies are not required. An overview based on a literature review is, thus, appropriate.

### IV.4 Clinical efficacy

#### Efficacy

A multi-centre, randomised, double-blind, placebo-controlled, parallel group multi-dose study was undertaken under fasting conditions to evaluate the efficacy of ‘Strefen Direct 8.75 mg Oromucosal Spray’ in over 500 patients aged 18-75 years old with sore throat due to upper respiratory tract infection.

The primary objective of this study was to evaluate the efficacy of Strefen Direct 8.75 mg Oromucosal Spray in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness, sore throat relief and sore throat pain intensity changes in patients treated with Strefen Direct 8.75 mg Oromucosal Spray or placebo. Functional measures of difficulty in swallowing and swollen throat were also assessed.

The secondary objective of this study was to determine additional patient/consumer benefits associated with Strefen Direct 8.75 mg Oromucosal Spray. These benefits were assessed by responses to a consumer questionnaire.

The primary efficacy endpoint was the area under the change from baseline curve (AUC) in throat soreness from 0-2 hours post dose ($\text{AUC}_{0-2h}$).
Key **secondary endpoints** included AUC from 0-3 and 0-6 hours post-dose for change from baseline in throat soreness, sore throat pain intensity, difficulty swallowing, swollen throat and sore throat pain relief from baseline. These criteria were also assessed at various individual time points from 5 minutes to 6 hours after dosing and (with the exception of change from baseline in sore throat pain intensity) at the end of Day 1, 24 hours after the first dose and at the end of Days 2 and 3. Patients’ overall treatment rating and patients’ satisfaction were assessed at three hours after dosing and at the end of Day 3. Other secondary endpoints related to the proportion of symptom-free patients at various time points, time to reporting moderate pain relief, consumption of trial medication and rescue medication (paracetamol) and responses to questions in a consumer questionnaire.

**Statistical Methods for Evaluation**

The primary efficacy endpoint, severity of throat soreness AUC\(_{0-2h}\), was analysed using the analysis of covariance (ANCOVA) with baseline severity of throat soreness as a covariate and factors for treatment group and centre. Treatment group differences were estimated using the least square means method and 95% confidence intervals (CIs) based on the means square error from the ANCOVA.

Throat soreness, sore throat pain intensity scale (STPIS), difficulty swallowing scale (DSS) and swollen throat scale (SwoTS) were analysed by the same ANCOVA model as the primary efficacy endpoint but with the relevant baseline value as the covariate in the model. The total of pain relief ratings (TOTPAR), overall spray usage, and overall rescue medication consumption outcomes were also analysed using this method, with baseline ‘severity of throat soreness’ as a covariate.

**Results**

The primary efficacy endpoint was severity of throat soreness AUC\(_{0-2h}\). The ANCOVA results for the intent to treat (ITT) population showed the treatment main effect was statistically significant (p-value < 0.0001) in favour of the Stafen Direct 8.75 mg Oromucosal Spray.

Similar results were obtained for the secondary endpoints which are summarised in the table below.

**Summary of secondary efficacy endpoints at 0 to 6 hours after the first dose (ITT population)**

<table>
<thead>
<tr>
<th></th>
<th>Stafen Direct 8.75 mg Oromucosal Spray (N=249)</th>
<th>Placebo Spray (N=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of throat soreness area under the change from baseline curve from 0 to 6 hours, AUC(_{0-6h})</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-2.14 (1.551)</td>
<td>-1.50 (1.385)</td>
</tr>
<tr>
<td>Difference between LS means (95% CI)</td>
<td>-0.66 (-0.91, -0.41)</td>
<td></td>
</tr>
<tr>
<td><strong>STPIS SPID(_{0-6h})</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-22.50 (17.894)</td>
<td>-15.64 (16.413)</td>
</tr>
<tr>
<td>Difference between LS means (95% CI)</td>
<td>-7.36 (-10.21, -4.52)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTPAR(_{0-6h})</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.24 (1.456)</td>
<td>2.47 (1.248)</td>
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<tr>
<td>Difference between LS</td>
<td>-0.77 (0.53, 1.00)</td>
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</table>
DSS AUC$_{0-6h}$
Mean (SD)  -22.50 (18.260)  -16.01 (15.451)
Difference between LS means (95% CI)  -6.82 (-9.64, -3.99)

SwoTS AUC$_{0-6h}$
Mean (SD)  -20.97 (18.897)  -13.80 (15.565)
Difference between LS means (95% CI)  -7.59 (-10.42, -4.77)

All analysis were done on n=249 for the active spray and n=256 for the placebo spray. P –values < 0.0001 for all of the above.

SPID – sum of pain intensity differences.

The figure below presents the AUC for change from baseline in throat soreness from 0-6 hours.

**Mean 0-6h Profile of change from baseline in throat soreness**

Overall, in severity of throat soreness, sore throat pain intensity, sore throat relief, difficulty in swallowing and swollen throat, the Strefen Direct 8.75 mg Oromucosal Spray showed an improvement in symptoms of sore throat, with the majority of comparisons showing a statistically significant difference between the two treatment groups in favour of Strefen Direct 8.75 mg Oromucosal Spray over placebo. This was the case for the time points up to 6 hours after the initial spray, and it extended up to the end of Day 3 following more sprays.
IV.5 Clinical safety

Bioequivalence studies

Pilot study
There were no serious adverse events or laboratory adverse events reported in this study and no subject was discontinued due to an adverse event (AE) occurrence.

A total of 18 AEs were reported by 8 (67%) subjects overall in this study, with the highest incidence (4 [33%] subjects) occurring following treatments B and D. Overall, AE reporting was minimal across treatments; the lowest incidence occurred following treatment C (1 [8%] subject), with 2 (17%) subjects reporting events following treatment A. The most common AE reported during the study was upper respiratory tract infection, 3 episodes overall following treatment B, which were considered by the PI to be not related to the study treatment. Overall, the PI considered 14 events to be unlikely to be related to the study treatment and 4 events to be not related, and considered 17 events to be mild in intensity and 1 event to be moderate (upper respiratory tract infection [treatment B]). Table 12.2.1 presents AE incidence and frequency of AEs by treatment.

Pivotal study
There were no serious adverse events or laboratory adverse events reported in this study and no subject was discontinued due to an adverse event (AE) occurrence.

A total of 12 AEs were reported by 9 (27%) subjects, with 6 (18%) subjects reporting 9 AEs following flurbiprofen 8.75 mg honey and lemon lozenge, 2 (6%) subjects reporting 2 AEs following Strefen Direct 8.75 mg Oromucosal Spray, and 1 (3%) subject reporting 1 AE following 8.75 mg/540 μL flurbiprofen Spray B. The most common AEs were headache and pharyngeal hypoesthesia, reported by 2 (6%) subjects each.

A total of two AEs were considered by the principal investigator of the study to be probably related to the study treatment, 1 to be possibly related, 4 to be unlikely to be related, and 5 to be unrelated. The principal investigator for the bioequivalence study considered 10 AEs to be mild in severity and 2 AEs to be moderate.

Efficacy study

Treatment emergent adverse events (TEAEs) are defined as AEs with an onset time of or following the start of treatment with study drug, or AEs starting before the start of treatment, but increasing in severity or relationship at the time of or following the start of treatment. AEs were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class (SOC).

A total of 31/249 (12.4%) patients in the Strefen Direct 8.75 mg Oromucosal Spray treatment group reported 41 TEAEs and 21/256 (8.2%) patients in the placebo spray treatment group reported 22 TEAEs.

The SOC with the most reported TEAEs was “Nervous system disorders” with 12 (12/249; 4.8%) in the Strefen Direct 8.75 mg Oromucosal Spray treatment group and six (6/256; 2.3%) in the placebo spray treatment group. The PT with the most TEAEs reported was “Headache” reported by seven patients (7/249; 2.8%) in the 8.75 mg Strefen Direct 8.75 mg Oromucosal Spray treatment group and six patients (6/256; 2.3%) in the placebo spray treatment group.
Three patients (1/249 [0.4%] in the Strefen Direct 8.75 mg Oromucosal Spray treatment group and 2/256 [0.8%] in the placebo spray treatment group) reported TEAEs that were severe. All three severe TEAEs were assessed as unlikely to be related to the study medication.

There were no TEAEs assessed as definitely related to study medication. There were 8/249 (3.2%) patients who reported TEAEs that were assessed as probably related to study medication. All these patients received Strefen Direct 8.75 mg Oromucosal Spray. A total of 18 patients (9/249 [3.6%] in the Strefen Direct 8.75 mg Oromucosal Spray group and 9/256 [3.5%] patients in the placebo spray group) reported TEAEs that were assessed as possibly related to study medication.

There was one patient who received Strefen Direct 8.75 mg Oromucosal Spray for whom study medication was permanently discontinued and who was withdrawn from the study due to TEAEs. One patient who received the placebo spray permanently discontinued study medication due to a TEAE.

No physical examinations or laboratory examinations were done as part of the safety assessment of this study. Oral temperature was taken at baseline, 180 minutes post first dose and at the follow-up visit. There were no safety issues identified as it was normal at all the endpoints and was similar between the two treatment groups.

There were no patients who reported serious adverse events (SAEs) or who died during the study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, 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 Strefen Direct 8.75mg Oromucosal Spray.

<table>
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<tr>
<th>Summary of safety concerns</th>
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| **Important identified risks** | Gastrointestinal disorders, particularly among elderly patients, and those with a history of gastrointestinal disease, such as ulcerative colitis, Crohn’s disease, bleeding, ulceration or perforation

Renal disorders – particularly among those patients with pre-existing renal insufficiency or prostaglandin-dependent conditions such as renal disease, dehydration, liver dysfunction, chronic heart failure and advanced age.

Nervous system disorders – particularly headache. |
| **Important potential risks** | Potential for drug interactions – particularly with other NSAIDs; anti-platelet agents such as acetylsalicylic acid; anticoagulants such as warfarin.

Use of the drug during pregnancy – particularly for those attempting to conceive, experience difficulty conceiving or undergoing fertility treatment, as well as women in their third trimester of pregnancy and breast-feeding women. |
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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</table>
| Gastrointestinal disorders – particular among elderly patients, and those with a history of gastrointestinal disease, such as ulcerative colitis, Crohn’s disease, bleeding, ulceration or perforation | To address this concern the SPC, section 4.3
‘Contraindications,’ which includes the following wording: ‘Contraindications: History of’ | None required: routine pharmacovigilance.                                                         |
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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</table>
| perforation.  | gastrointestinal bleeding or perforation, severe colitis, hemorrhagic or haematopoietic disorders related to previous NSAID therapy.  
Additional warnings within SPC section 4.4 'special warnings and precautions for use,' with the following wording:  
"NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8). Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly, however this effect is not usually seen with short term limited use products such as flurbiprofen spray. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) to their healthcare professional. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding. |
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<th>Safety concern</th>
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<th>Additional risk minimisation measures</th>
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<td>such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5), if GI bleeding or ulceration occurs in patients receiving flurbiprofen, the treatment should be withdrawn.</td>
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<td>Warnings within 4.8 'undesirable effects,' tabulating the frequency and adverse events of Gastrointestinal disorders.</td>
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<td>In addition, section 2 of the Product Information Leaflet states this product should not be consumed if the patient has stomach ulcers or bleeding, or severe colitis. Section 4 states that patients should stop taking the product if they develop any of these symptoms.</td>
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<td>To monitor this concern within monitoring of the post-marketing information, data collection and management, safety reporting writing, up-to-date product literature information, monitoring of relevant medical literature journals, signal detection and coordination and networking, will be sufficient.</td>
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<tr>
<td>Renal disorders – particular among those patients with pre-existing renal insufficiency or prostaglandin-dependent conditions such as renal disease, dehydration, liver dysfunction, chronic heart failure and advanced age.</td>
<td>To address this concern the SPC, section 4.3 'contraindications,' which includes the following wording: &quot;Contraindications: Severe heart failure, renal failure or hepatic failure.&quot;</td>
<td>None required: routine pharmacovigilance.</td>
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<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td><em>Additional warnings within SPC section 4.4 ‘special warnings and precautions for use,’ with the following wording: “NSAIDs have been reported to cause nephrotoxicity in various forms including interstitial nephritis, nephrotic syndrome and renal failure. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly, however, this effect is not usually seen with short term, limited use products such as flurbiprofen spray.”</em></td>
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<td>In addition, section 2 of the Product Information Leaflet states this product should not be consumed if the patient has heart, kidney or liver problems. Section 4 states that patients should stop taking the product if they develop any of these symptoms.</td>
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<td>To monitor this concern within monitoring of the post-marketing information, data collection and management, safety reporting writing, up-to-date product literature information, monitoring of relevant medical literature journals, signal detection and coordination and networking, will be sufficient.</td>
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<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
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<td>Nervous System disorders – particularly headache.</td>
<td>To address this concern the SPC, section 4.4 'special warnings and precautions for use', with the following wording: &quot;In the event of prolonged use of analgesics or use beyond the regulations headache may occur, which must not be treated with increased doses of the medicinal product.&quot;</td>
<td>None required: routine pharmacovigilance.</td>
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<td>Section 4.8 'undesirable effects' and warnings within product labeling are in place, tabulating the frequency and adverse events of surrounding nervous system disorders.</td>
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<td>In addition, section 2 of the Product Information Leaflet states this product should not be consumed if the patient has regular headaches. Section 4 states that patients should stop taking the product if they develop a headache, which is stated as a common possible side effect.</td>
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<td>To monitor this concern within monitoring of the post-marketing information, data collection and management, safety reporting writing, up-to-date product literature information, monitoring of relevant medical literature journals, signal detection and coordination and networking, will be sufficient.</td>
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<td>Potential for drug interactions – particularly with other NSAIDS; anti-platelet agents such as acetylsalicylic acid; anticoagulants such as warfarin.</td>
<td>To address this concern within the SPC, section 4.4 'special warnings and precautions for use', with the following wording: &quot;The use of flurbiprofen spray</td>
<td>None required: routine pharmacovigilance.</td>
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<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
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<td>with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided.</td>
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Section 4.5 ‘interactions with other medicinal products and other forms of interaction’, tabulating the medicinal products which should be avoided in combination with flurbiprofen, and those that should be used in caution with flurbiprofen.

In addition, section 2 of the Product Information Leaflet states this product should not be consumed if the patient is taking any of the listed medicines.

To monitor this concern within monitoring of the post-marketing information, data collection and management, safety reporting writing, up-to-date product literature information, monitoring of relevant medical literature journals, signal detection and coordination and networking, will be sufficient.

Use of the drug during pregnancy – particularly for those women attempting to conceive, experience difficulty conceiving or undergoing fertility treatment, as well as women in their third trimester of pregnancy and breast-feeding women.

To address this concern within the SPC, section 4.3 ‘contraindications,’ which includes the following wording:

“Contraindications: Last trimester of pregnancy.”

Additional warnings within SPC section 4.6 ‘pregnancy and lactation,’ with the following wording:

“Inhibition of prostaglandin...”
<table>
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tr>
<td>synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, flurbiprofen should not be given unless clearly necessary. If flurbiprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:</td>
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**IV.7 Discussion on the clinical aspects**

The application contains an adequate review of published clinical data and the bioequivalence has been shown between the test and reference products. The additional clinical study data has also demonstrated efficacy and safety of Strefen Direct 8.75mg Oromucosal Spray.

Sufficient clinical information has, therefore, been submitted regarding this application. When used as indicated, Strefen Direct 8.75mg Oromucosal Spray has a favourable benefit-to-risk ratio.

The grant of a marketing authorisation is recommended for this application.
V  User consultation
The package leaflet 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 PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The application contains an adequate review of published clinical data and bioequivalence has been shown between the test product and an equivalent strength lozenge. The additional efficacy study data has also demonstrated efficacy of Strefen Direct 8.75mg Oromucosal Spray. The safety data from all studies submitted are in line with the typical safety profile seen for products of this kind.

Sufficient clinical information has, therefore, been submitted regarding this application. Strefen Direct 8.75mg Spray contains a widely used and well-known active substance, flurbiprofen, which has a long history of established favourable risk-benefit profile. The benefit/risk assessment is, therefore, considered to be positive.
Annex – Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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