Public Assessment Report

Scientific discussion

Ibuprofen Chanelle Medical 200 mg and 400 mg, soft capsules

(ibuprofen)

NL/H/4401/001-002/DC

Date: 28 August 2019

This module reflects the scientific discussion for the approval of Ibuprofen Chanelle Medical 200 mg and 400 mg, soft capsules. The procedure was finalised at 22 May 2019. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ibuprofen Chanelle Medical 200 mg and 400 mg, soft capsules, from Chanelle Medical.

The product is indicated for the short-term symptomatic treatment of mild to moderate pain and/or fever.

The 200 mg strength is indicated for use in adults, adolescents and children from 20 kilograms body weight (7 years and older) and the 400 mg strength is indicated for use in adults and adolescents from 40 kilograms body weight (12 years and older).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nurofen Express 342 mg and 684 mg, caplets which has been registered in the United Kingdom by Reckitt Benckiser since 17 January 2006. In the Netherlands, the product from the United Kingdom is used as European Reference Product.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Spain, France, Ireland, Italy, Poland, Portugal and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Chanelle Medical 200 mg is a opaque, red, oval soft capsule with “200” printed in white ink. Each soft capsule contains 200 mg of ibuprofen (equivalent to 342 mg ibuprofen lysine).

Chanelle Medical 400 mg is a opaque, red, oblong soft capsule with “400” printed in white ink. Each soft capsule contains 400 mg of ibuprofen (equivalent to 684 mg ibuprofen lysine).

The soft capsules are packed in transparent PVC/PE/PVDC-AU blisters.

The excipients are:

Capsule content - medium chain triglycerides, lecithin (soybean), purified water, sorbitol liquid partially dehydrated (E420), titanium dioxide in sorbitol liquid; 1:2 w/w (E171) and FD&C red #40; allura red (E129)

Capsule shell – gelatin (bloom 150)
**Printing Ink** - purified water, titanium dioxide (E171), propylene glycol (E1520), isopropyl alcohol and HPMC 2910/hypromellose

### II.2 Drug Substance

The active substance is racemic ibuprofen lysine, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). The racemic active substance is a white to off-white powder and is highly soluble in water at a pH above 6.8. Only one polymorphic form is reported for racemic ibuprofen lysine at room temperature. The active substance is not hygroscopic.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

**Manufacturing process**

The manufacturing process is a two step synthesis followed by salt formation. No class I solvents are used. The active substance is adequately characterised. The specifications of the starting material, reagents and solvents are adequate.

**Quality control of drug substance**

The active substance specification is established in-house by the MAH and is considered adequate to control the quality. Differences in the specifications between the drug product manufacturer and the ASMF holder are the maximum limit of the residual solvents and the particle size distribution. The specification is acceptable; all tests are according to requirements and applicable guidance. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

**Stability of drug substance**

Stability data on the active substance have been provided for three commercial batches stored at 30°C/70%RH (60 months) and 40°C/75% RH (6 months). Under both conditions no upward or downward trend for any of the tested parameters is observed. Based on the data submitted, a retest period could be granted of 48 months.

### II.3 Medicinal Product

**Pharmaceutical development**

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The manufacturing process is based on previous
experience within the finished product manufacturer on the manufacture of soft gelatin capsules, particularly related to the manufacture of suspension based formulations. A bioequivalence study has been performed between the test and reference products of the highest strength (400 mg ibuprofens equivalent to 684 mg ibuprofen lysine). For the lower strength (200 mg ibuprofen equivalent to 342 mg ibuprofen lysine) an biowaiver has been requested. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process is a standard process and has been validated according to relevant European guidelines. The steps include medicine fill preparation, gel mass preparation, encapsulation, drying and post production. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled batches of the 2.5 mg, 5 mg and 10 mg strengths and three pilot scaled batches for.
The presented manufacturing process validation protocol provides details of sampling plans and acceptance criteria for the attributes measured, which are considered acceptable. In accordance with EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1, no validation data will be requested at submission. The MAH commits that where the results obtained show significant deviations from those expected, the regulatory authorities will be informed immediately. In such cases, corrective actions will be proposed and any proposed changes to the manufacturing process will receive appropriate regulatory approval by way of variation.

Control of excipients
The excipients and packaging materials used for the drug product are well known. Functionality-related characteristics of the excipients were discussed. The 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 description, identification, dissolution, uniformity of dosage units, assay, degradation, disintegration, microbiological test. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches of each strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. All results remained within specifications limits and no specific trends were observed. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC on the label.
Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All excipients except for gelatine, are of non-animal origin. A declaration from all the excipient suppliers has been provided. For gelatine, copies of EDQM certificates of suitability from the current gelatin suppliers have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ibuprofen Chanelle Medical has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

This product is a generic formulation of Nurofen Express which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Chanelle Medical 400 mg, soft capsules (Chanelle Medical, Ireland) is compared with
the pharmacokinetic profile of the reference product Nurofen Express 684 mg, caplets (Reckitt Benckiser, UK).

The choice of the reference product in the bioequivalence study is justified as the reference product was authorised in the EEA through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

**Biowaiver**

Biowaiver is applied for the lower 200 mg strength. All products were manufactured by the same process and the composition of the different strengths is qualitatively the same. The MAH provided information showing that the content of the 200 mg (342 ibuprofen lysine) and 400 mg (684 mg ibuprofen lysine) capsules is dose-proportional. Only difference in the ratio capsule weight vs content were noted, for which proportionality however is not required. The dose-linearity was sufficiently discussed by the MAH based on literature. Approximate dose-linear pharmacokinetics has been demonstrated for ibuprofen between 200 and 400 mg.

The MAH has provided the requested bootstrap analyses, using the data obtained at 50 rpm and 900 ml at pH 1.2, 4.5 and 6.8. Based on the lower 90% CI limits, comparative dissolution at pH 1.2 and 6.8 at 50 rpm in 900 ml has been demonstrated. For pH 4.5, the MAH provided a lower limit of 50 (rounded from 49.61).

In conclusion, comparative dissolution between the 200 mg and 400 mg strengths has been sufficiently demonstrated. Therefore, a biowaiver for the additional 200 mg can be granted.

**Bioequivalence study**

**Design**

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male and female subjects, aged 19-59 years. Each subject received a single dose (400 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 200 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 16 days.

Blood samples were collected at pre-dose and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, and 12 hours after administration of the products.

The design of the study is acceptable. The product may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ibuprofen. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.
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
One subject was withdrawn from the study due to common cold. Therefore, 25 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of S-(-)-ibuprofen under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=25</th>
<th>( \text{AUC}_{0-t} ) (ng.h/ml)</th>
<th>( \text{AUC}_{0-\infty} ) (ng.h/ml)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( t_{\text{max}} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>71.56 ± 26.25</td>
<td>74.36 ± 30.67</td>
<td>25.07 ± 5.48</td>
<td>0.75 (0.33 - 1.00)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>73.00 ± 25.88</td>
<td>75.77 ± 29.86</td>
<td>24.43 ± 5.86</td>
<td>0.50 (0.33 - 1.50)</td>
<td></td>
</tr>
</tbody>
</table>

\*Ratio (90\% CI)

0.98 (0.93 – 1.03) -- 1.03 (0.97 – 1.10) --

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( C_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration

*ln-transformed

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of R-(+)-ibuprofen under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=25</th>
<th>( \text{AUC}_{0-t} ) (ng.h/ml)</th>
<th>( \text{AUC}_{0-\infty} ) (ng.h/ml)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( t_{\text{max}} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>67.15 ± 17.73</td>
<td>67.75 ± 17.79</td>
<td>30.99 ± 7.34</td>
<td>0.75 (0.33 - 1.00)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>73.48 ± 18.37</td>
<td>74.14 ± 18.54</td>
<td>30.29 ± 7.07</td>
<td>0.50 (0.33 - 1.50)</td>
<td></td>
</tr>
</tbody>
</table>

\*Ratio (90\% CI)

0.91 (0.86 – 0.96) -- 1.02 (0.95 – 1.09) --

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( C_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration

*ln-transformed values
Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ibuprofen Chanelle Medical is considered bioequivalent with Nurofen Express.

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

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ibuprofen Chanelle Medical.

<table>
<thead>
<tr>
<th>Table 3. Summary table of safety concerns as approved in RMP</th>
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<tbody>
<tr>
<td>Important identified risks</td>
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<tr>
<td>Important potential risks</td>
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<tr>
<td>Missing information</td>
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</tbody>
</table>

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 Nurofen Express. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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 test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the
following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

for Ibuprofen Chanelle Medical 200 mg and 400 mg, soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Nurofen Express 342 mg and 684 mg, caplets. Nurofen Express is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Ibuprofen Chanelle Medical with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 May 2019.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Procedure number</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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