Public Assessment Report

Scientific discussion

Ibuprofen Sandoz 200 mg and 400 mg, capsules, soft

(ibuprofen)

NL/H/2810/001-002/MR

Date: 28 January 2016

This module reflects the scientific discussion for the approval of Ibuprofen Sandoz 200 mg and 400 mg, capsules, soft. The procedure was finalised on 14 February 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
I. INTRODUCTION

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

The product is indicated for the short-term symptomatic treatment of mild to moderate pain, such as headache, dental pain, period pain and fever and pain in the common cold. The 400 mg strength is also indicated for acute migraine headache with or without aura.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Nurofen 200 mg liquicaps, authorised in the UK by Reckitt Benckiser healthcare International Ltd since 1999, and Advil 400 mg capsules registered in Spain by Wyeth Farma S.A. since 2002.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Croatia, Czech Republic, Finland, Germany (only 400 mg), Greece, Hungary (only 400 mg), Ireland, Italy, Luxembourg, Romania, Slovakia, Slovenia and Spain (only 400 mg).

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Sandoz 200 mg is a clear oval shaped soft gelatin capsules containing colourless to pale yellow coloured, transparent, viscous liquid, printed ’200’ in black colour on capsule shell.

Ibuprofen Sandoz 400 mg is a clear oval shaped soft gelatin capsules containing colourless to pale yellow coloured, transparent, viscous liquid, printed ’400’ in black colour on capsule shell.

The soft capsules are packed in PVdC/Aluminium blisters.

The excipients are:
- capsule content 200 mg - macrogol 400 (E1521), sorbitol solution (E420), sorbitan oleate (E494), potassium hydroxide (E525)
- capsule content 400 mg - macrogol400 (E1521), sorbitan oleate (E494), povidone K-30, potassium hydroxide (E525)
- capsule shell - gelatin (E441), macrogol 400 (E1521), sorbitol solution (E420), medium-chain triglycerides.

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ibuprofen is practically insoluble in water, very soluble in alcohol, in acetone, in methanol and in chloroform and slightly soluble in ethyl acetate. Ibuprofen is a racemic mixture of two isomers.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.
Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full scaled batch. Given the fact that a CEP is available this is considered acceptable.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. For both strengths an initial formulation was tested against the innovator. During the development the composition and process parameters were optimised several times until the final manufacturing formula and method were obtained.

The composition of the batches used in the bioequivalence studies are identical to the proposed composition and the optimised manufacturing process was used. The MAH provided the comparative dissolution profiles of the ibuprofen soft gelatin 400 mg and 200 mg capsules with the Dutch reference medicines Advil® liquid-caps 400 and Nurofen liquid-caps 200. Although the similarity values do not display similarity, the bioequivalence study has demonstrated bioequivalence indisputably. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been described in sufficient detail and includes steps of mixing, heating, melting and encapsulation. It is seen as a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches for the 200 mg strength and three pilot-scale batches for the 400 mg strength. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. and the specifications are acceptable. The non-compendial excipients are the pharmaceutical ink for printing on the capsule shell. The components of the ink are well-known and may be safely used for printing of drug products. A GMP certificate from the vendor has been included in the dossier.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units, loss on drying, dissolution rate, assay, related substances, residual solvent and microbiological purity. With the exception of the specification for the assay for the 400 mg capsules the release and end of shelf-life specifications are identical. The specifications are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for one batch of the 200 mg and for three batches of the 400 mg capsules, demonstrating compliance with the release specification.

Stability of drug product
For the 200 mg capsules stability data on the product have been provided for three pilot-scale batches stored at 25°C/60%RH (36 months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months) in all packaging materials. When stored at 40°C/75%RH the dissolution test fails during analysis of 3 months samples. The twelve months stability data at 30°C/65%RH and the three years stability data at 25°C/60%RH are satisfactory for the stability pack sizes. No changes in any of the parameters are observed.

For the 400 mg capsules stability data on the product have been provided for three pilot-scale batches stored at 25°C/60%RH (24 months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months) in all packaging materials. When stored at 40°C/75%RH the dissolution test fails during analysis of 3
months samples. The twelve months stability data at 30°C/65%RH and the three years stability data at 25°C/60%RH are satisfactory for the stability pack sizes. No changes in any of the parameters are observed.

Based on the stability data it is concluded that the claimed shelf-life for the 200 mg and 400 mg ibuprofen soft gelatin capsules is justified. A shelf-life of 36 months, when stored below 30°C was granted. The product does not need to be protected from light.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

Gelatin is the only excipient obtained from animal origin. A CEP of gelatine as well as a certificate with respect to the TSE/BSE safety is included.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Ibuprofen Sandoz 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 Ecotoxicity/environmental risk assessment (ERA)**

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

**III.2 Discussion on the non-clinical aspects**

This product is a generic formulation of Advil and Nurofen 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 two bioequivalence studies, which are discussed below.

**IV.2 Pharmacokinetics**

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test products Ibuprofen Sandoz 200 mg and 400 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Nurofen 200 mg liquicapsules (Crookes Healthcare Limited UK) and Advil Liquid Caps 400 mg (Consumer Healthcare, the Netherlands).

The choice of the reference products in the bioequivalence studies has been justified. The qualitative and quantitative composition of the Advil liquid caps 400 mg used in the bioequivalence study and of
the EU reference product Advil 400 mg capsulas blandas from Wyeth Farma Spain has been compared. Taking into account the similarity in composition, and the fact that both products belong to the same Global Marketing Authorisation, it is justified to use the results of the biostudy performed with Advil 400 mg registered in the Netherlands for bridging to the (preclinical and clinical) data included in the dossier of the EU reference product Advil authorised in Spain.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Bioequivalence study I – 200 mg

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (20 males and 4 females), aged 20-37 years. Each subject received a single dose (200 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00 and 24.00 hours after administration of the products.

The overall study design is considered acceptable taking into account the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless of food intake, a study under fasting conditions is justified.

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
Two subjects were withdrawn from the study due to positive urine drug abuse test on the enrolment day of the second period. A total of 22 subjects completed the clinical phase of the study successfully. Plasma samples of these 22 subjects were included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of ibuprofen under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=22</th>
<th>AUC0-t (µg.h/ml)</th>
<th>AUC0-∞ (µg.h/ml)</th>
<th>Cmax (µg/ml)</th>
<th>tmax (h)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>65.24 ± 17.61</td>
<td>68.07 ± 17.98</td>
<td>27.34 ± 6.42</td>
<td>0.50</td>
<td>1.75 ± 0.42</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>66.92 ± 14.43</td>
<td>69.74 ± 14.63</td>
<td>29.88 ± 5.19</td>
<td>0.50</td>
<td>1.74 ± 0.37</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>0.97 (0.93 – 1.02)</td>
<td>0.97 (0.93 – 1.02)</td>
<td>0.92 (0.85 – 0.98)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

CV (%) | 8.5 | 8.1 | 13.6 | -- | -- |

AUC0-∞: area under the plasma concentration-time curve from time zero to infinity
AUC0-t: area under the plasma concentration-time curve from time zero to t hours
Cmax: maximum plasma concentration
tmax: time for maximum concentration
t1/2: half-life
CV: coefficient of variation

*ln-transformed values

Bioequivalence study II – 400 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (20 males and 4 females), aged 19-39 years. Each subject received a single dose (400 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.16 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00 and 24.00 hours after administration of the products.

The study design is considered adequate for establishing bioequivalence between test and reference product. The procedures followed for a fasting condition and a wash-out period of 7 days (i.e. at least 5 terminal half-lives to exclude carry-over effects) is agreed.

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
Two subjects withdrew from the study before the second period due to personal reasons and one subject withdrew on the first day of the second period due to an adverse event. One subject dropped out after 12 hours of blood sample collection in Period II due to personal reasons. As the latter subject missed only the 24 hour sample in Period II, his plasma samples were also included in the analytical and statistical analysis. A total of 21 subjects were therefore included in the analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of ibuprofen under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t µg.h/ml</th>
<th>AUC0-∞ µg.h/ml</th>
<th>Cmax µg/ml</th>
<th>tmax h</th>
<th>t1/2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>109.1 ± 18.1</td>
<td>111.5 ± 48.9</td>
<td>38.6 ± 11.1</td>
<td>0.67</td>
<td>0.33 – 2.5</td>
</tr>
<tr>
<td>Reference</td>
<td>112.3 ± 18.5</td>
<td>114.1 ± 19.5</td>
<td>41.1 ± 8.3</td>
<td>0.83</td>
<td>0.50 – 3.0</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

|            | (0.94 – 1.02) | (0.94 – 1.03) | (0.82 – 1.04) | --     | --     |

CV (%) -- -- -- -- --

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration
tmax time for maximum concentration
t1/2 half-life
CV coefficient of variation

*ln-transformed values

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ibuprofen Sandoz 200 mg and 400 mg are considered bioequivalent with Nurofen 200 mg liquicapsules and Advil Liquid Caps 400 mg.

The MEB has been assured that the bioequivalence studies have 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

- **Summary table of safety concerns as approved in RMP**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding, ulceration and perforation</td>
<td>Medication overuse headache (MOH)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Second myocardial infarction</td>
</tr>
<tr>
<td>Exacerbation of ulcerative colitis and Crohn’s disease</td>
<td>Impaired female fertility</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>Use during 1st and 2nd pregnancy trimester</td>
</tr>
<tr>
<td>Cerebrovascular accident (CVA)</td>
<td></td>
</tr>
<tr>
<td>Severe skin reactions (including exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis)</td>
<td></td>
</tr>
<tr>
<td>Renal toxicity/renal failure</td>
<td></td>
</tr>
<tr>
<td>Use during third trimester of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as aspirin</td>
<td></td>
</tr>
<tr>
<td>Interaction with antihypertensive agents (e.g. diuretics, beta-blockers, ACE inhibitors, AR-II antagonists, etc.)</td>
<td></td>
</tr>
<tr>
<td>Use by elderly</td>
<td></td>
</tr>
<tr>
<td>Use by patients with (history of) bronchial asthma</td>
<td></td>
</tr>
<tr>
<td>Important missing information</td>
<td>Important missing information</td>
</tr>
<tr>
<td>Off-label use of concomitant NSAIDs</td>
<td>Off-label use of concomitant NSAIDs</td>
</tr>
<tr>
<td>Use by children &lt; 12 years of age</td>
<td>Use by children &lt; 12 years of age</td>
</tr>
<tr>
<td>Use for &gt; 14 days</td>
<td>Use for &gt; 14 days</td>
</tr>
<tr>
<td>Lactation</td>
<td>Lactation</td>
</tr>
</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 products Nurofen and Advil soft capsules. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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. Two stages of testing were
performed, each involving 10 subjects. The participants were questioned about the leaflet in an 
evaluation and problem-seeking test. The questionnaire for this user test contained 14 questions 
specific to the key safety issues of ibuprofen and 1 question general to the format of the leaflet. The 
questions sufficiently address the key safety messages.

The original PL has been provided in the report. After the first round the criteria as set in the 
readability guideline were not met. Suggestions for improvement of the leaflet were given and the PL 
was amended except for the proposals not in line with the QRD template.

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

Ibuprofen Sandoz 200 mg and 400 mg, capsules, soft have a proven chemical-pharmaceutical quality 
and are generic forms of Nurofen 200 mg and Advil 400 mg soft capsules. Nurofen and Advil 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. In the Netherlands, Ibuprofen Sandoz 200 mg and 
400 mg, capsules, soft was authorised on 13 April 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a 
written procedure. The concerned member states, on the basis of the data submitted, considered that 
essential similarity has been demonstrated for Ibuprofen Sandoz with the reference product, and have 
therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a 
positive outcome on 14 February 2015.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<tbody>
<tr>
<td>Addition of a secondary packager.</td>
<td>NL/H/2810/001-002/IA/G</td>
<td>IA/G</td>
<td>16-7-2015</td>
<td>17-8-2015</td>
<td>Approval</td>
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<tr>
<td>Addition of a batch release site without testing.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Change in the (invented) name of the medicinal product in Slovenia.</td>
<td>NL/H/2810/001-002/IB</td>
<td>IB</td>
<td>8-9-2015</td>
<td>10-11-2015</td>
<td>Approval</td>
<td>No</td>
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<tr>
<td>Change in immediate packaging of the finished product</td>
<td>NL/H/2810/001-002/IA/004</td>
<td>IA</td>
<td>13-11-2015</td>
<td>13-12-2015</td>
<td>Approval</td>
<td>No</td>
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<td>Change in the (invented) name of the medicinal product in Bulgaria.</td>
<td>NL/H/2810/001-002/IB/005</td>
<td>IB</td>
<td>1-12-2015</td>
<td>31-12-2015</td>
<td>Approval</td>
<td>No</td>
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<td>Addition of a batch control/testing site.</td>
<td>NL/H/2810/001-002/IA/006/G</td>
<td>IA</td>
<td>5-1-2016</td>
<td>13-1-2016</td>
<td>Approval</td>
<td>No</td>
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