Public Assessment Report

Decentralised Procedure

IBUPROFEN 200MG FILM-COATED TABLETS
IBUPROFEN 400MG FILM-COATED TABLETS

(ibuprofen)

Procedure No: UK/H/4780/001-002/DC

UK Licence No: PL 16028/0156-0157

Galpharm Healthcare Limited
This is a summary of the public assessment report (PAR) for Ibuprofen 200 mg Film-coated Tablets (PL 16028/0156) and Ibuprofen 400 mg Film-coated Tablets (Pl 16028/0157). It explains how Ibuprofen 200 mg and 400 mg Film-coated Tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Ibuprofen 200 mg and 400 mg Film-coated Tablets.

For practical information about using Ibuprofen 200 mg and 400 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ibuprofen 200 mg and 400 mg Film-coated Tablets and what are they used for?

Ibuprofen 200 mg and 400 mg Film-coated Tablets are ‘generic medicines’. This means that Ibuprofen 200 mg and 400 mg Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Brufen 200 mg and 400 mg tablets.

Ibuprofen 200 mg and 400 mg Film-coated Tablets are used for the short term relief of mild to moderate pain, such as headache, period pain, dental pain, and fever and pain associated with the common cold.

How are Ibuprofen 200 mg and 400 mg Film-coated Tablets used?

These medicines can be obtained without a prescription.

How do Ibuprofen 200 mg and 400 mg Film-coated Tablets work?

Ibuprofen 200 mg and 400 mg Film-coated Tablets contain the active ingredient ibuprofen. Ibuprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which work to reduce pain and fever.

How have Ibuprofen 200 mg and 400 mg Film-coated Tablets been studied?

Because Ibuprofen 200 mg and 400 mg Film-coated Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Brufen 200 mg and 400 mg tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Ibuprofen 200 mg and 400 mg Film-coated Tablets?

Because Ibuprofen 200 mg and 400 mg Film-coated Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and risks are taken as being the same as the reference medicines.

Why are Ibuprofen 200 mg and 400 mg Film-coated Tablets approved?

It was concluded that, in accordance with EU requirements, Ibuprofen 200 mg and 400 mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Brufen 200 mg and 400 mg tablets. Therefore, the view was that, as for Brufen 200 mg and 400 mg tablets, the benefit outweighs the identified risk.
What measures are being taken to ensure the safe and effective use of Ibuprofen 200 mg and 400 mg Film-coated Tablets?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Ibuprofen 200 mg and 400 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Ibuprofen 200 mg and 400 mg Film-coated Tablets

The Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Sweden, Slovakia and the UK agreed to grant Marketing Authorisations for Ibuprofen 200 mg and 400 mg Film-coated Tablets on 10 September 2013. Marketing Authorisations were granted in the UK on 10 October 2013.

The full PAR for Ibuprofen 200 mg and 400 mg Film-coated Tablets follows this summary. For more information about treatment with Ibuprofen 200 mg and 400 mg Film-coated Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2013.
TABLE OF CONTENTS

Module 1: Information about initial procedure .......................................................... Page 5
Module 2: Summary of Product Characteristics ...................................................... Page 6
Module 3: Patient Information Leaflet ................................................................. Page 7
Module 4: Labelling .............................................................................................. Page 8
Module 5: Scientific discussion during initial procedure ........................................ Page 12

I  Introduction
II  About the product
III  Scientific overview and discussion
   III.1  Quality aspects
   III.2  Non-clinical aspects
   III.3  Clinical aspects
IV  Overall conclusion and benefit-risk assessment

Module 6: Steps taken after initial procedure ....................................................... Page 20
### Module 1

**Information about initial procedure**

| **Product Name** | Ibuprofen 200 mg Film-coated Tablets  
Ibuprofen 400 mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Ibuprofen</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>200 mg and 400 mg</td>
</tr>
</tbody>
</table>
| **MA Holder** | Galpharm Healthcare Limited  
Hugh House  
Upper Cliffe Road  
Dodworth Business Park  
Dodworth  
South Yorkshire S75 3SP  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Sweden and Slovakia |
| **Procedure Number** | UK/H/4780/001/DC  
UK/H/4780/002/DC |
| **Timetable** | Day 210 – 10 September 2013 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the approved label text for Ibuprofen 200 mg Film-coated Tablets (PL 16028/0156). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
<tr>
<td>1.  NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Ibuprofen 200 mg Film-coated Tablets</td>
</tr>
<tr>
<td>2.  STATEMENT OF ACTIVE SUBSTANCES</td>
</tr>
<tr>
<td>Each film-coated tablet contains ibuprofen 200mg.</td>
</tr>
<tr>
<td>3.  LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>Also contains 128mg lactose monohydrate per film-coated tablet. See enclosed leaflet for further information.</td>
</tr>
<tr>
<td>4.  PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>Film-coated Tablet. Pack sizes of 6, 8, 10, 12, 16, 20, 24, 30, 48, 50, 96 or 100 tablets.</td>
</tr>
<tr>
<td>5.  METHOD AND ROUTES OF ADMINISTRATION</td>
</tr>
<tr>
<td>For oral use.</td>
</tr>
<tr>
<td>6.  SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td>7.  OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8.  EXPIRY DATE</td>
</tr>
<tr>
<td>&lt;To be overprinted in the format MM/YYYY&gt;</td>
</tr>
<tr>
<td>9.  SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td>Do not store above 25°C. Keep in the original container in order to protect from light and moisture.</td>
</tr>
<tr>
<td>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>No special precautions</td>
</tr>
<tr>
<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Galpharm Healthcare Limited</td>
</tr>
</tbody>
</table>
MARKETING AUTHORISATION NUMBER(S)
PL 16028/0156

BATCH NUMBER
>To be overprinted>

GENERAL CLASSIFICATION FOR SUPPLY
Pharmacy (P)

INSTRUCTIONS ON USE
For short term relief of mild to moderate pain such as headache, dental pain, period pain and fever and pain associated with the common cold.

Adults, and adolescents weighing from 40 kg (12 years old and above): Take 1 or 2 tablets with water, up to 3 times a day, as required. Leave at least 4 hrs between 200 mg doses or 6 hrs between 400 mg doses. Do not exceed 6 tablets in 24 hours.

Do not give to adolescents weighing under 40 kg or children under 12 years.

Please read the package leaflet carefully before use.
Do not exceed the stated dose.
Take the lowest effective dose needed to relieve your symptoms, as this product is intended for short term use only. Talk to your doctor or pharmacist if your symptoms worsen or you need to take these tablets for more than 3 days when you have a fever or 4 days when you are suffering from pain.

INFORMATION IN BRAILLE.
Ibuprofen 200 mg Film-coated Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER FOIL

NAME OF THE MEDICINAL PRODUCT
Ibuprofen 200 mg Film-coated Tablets

NAME OF THE MARKETING AUTHORISATION HOLDER
Galpharm Healthcare Limited

EXPIRY DATE
>To be embossed in the format MM/YYYY>

BATCH NUMBER
>To be embossed>

OTHER
Ibuprofen
Press tablets through from other side
The following text is the approved label text for Ibuprofen 400 mg Film-coated Tablets (PL 16028/0157). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Ibuprofen 400 mg Film-coated Tablets</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCES</td>
</tr>
<tr>
<td>Each film-coated tablet contains ibuprofen 400mg</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>Also contains 80mg lactose monohydrate per film-coated tablet. See enclosed leaflet for further information.</td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>Film-coated Tablet. Pack sizes of 6, 8, 10, 12, 16, 20, 24, 30, 48, 50, 96 or 100 tablets.</td>
</tr>
<tr>
<td>5. METHOD AND ROUTES OF ADMINISTRATION</td>
</tr>
<tr>
<td>For oral use.</td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>&lt;To be overprinted in the format MM/YYYY&gt;</td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td>Do not store above 25°C. Keep in the original container in order to protect from light and moisture.</td>
</tr>
<tr>
<td>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>No special precautions</td>
</tr>
<tr>
<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Galpharm Healthcare Limited</td>
</tr>
</tbody>
</table>
12. MARKETING AUTHORISATION NUMBER(S)

PL 16028/0157

13. BATCH NUMBER

<To be overprinted>

14. GENERAL CLASSIFICATION FOR SUPPLY

Pharmacy (P)

15. INSTRUCTIONS ON USE

For short term relief of mild to moderate pain such as headache, dental pain, period pain, and fever and pain associated with the common cold.

Adults and adolescents weighing from 40 kg (12 years old and above): Take 1 tablet with water, up to 3 times a day, as required. Leave at least 6 hours between doses. Do not exceed 3 tablets in 24 hours.

Do not give to adolescents weighing under 40 kg or children under 12 years.

Please read the package leaflet carefully before use. Do not exceed the stated dose. Take the lowest effective dose needed to relieve your symptoms, as this product is intended for short term use only. Talk to your doctor or pharmacist if your symptoms worsen or you need to take these tablets for more than 3 days when you have a fever or 4 days when you are suffering from pain.

16. INFORMATION IN BRAILLE.

Ibuprofen 400 mg Film-coated Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400 mg Film-coated Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Galpharm Healthcare Limited

3. EXPIRY DATE

<To be embossed in the format MM/YYYY>

4. BATCH NUMBER

<To be embossed>

5. OTHER

Ibuprofen
Press tablets through from other side
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Ibuprofen 200 mg and 400 mg Film-coated Tablets (PL 16028/0156-0157; UK/H/4780/001-002/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and The Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Sweden and Slovakia as Concerned Member States (CMS).

These products can be obtained without a prescription at a pharmacy (legal classification P).

These applications were made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB), which were granted marketing authorisations in Sweden on 14 March 1975.

Ibuprofen 200 mg and 400 mg Film-coated Tablets are indicated for short-term symptomatic treatment of mild to moderate pain, such as headache, dysmenorrhea (period pain), dental pain, and fever and pain in the common cold. These products contain the active substance ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and anti-pyretic properties.

No non-clinical studies were conducted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence studies were performed, which compared the pharmacokinetics of the test products Ibuprofen 200 mg and 400 mg Film-coated Tablets to those of the reference products Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of procedure on 10 September 2013. After a subsequent national phase, marketing authorisations were granted in the UK on 10 October 2013.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Ibuprofen 200 mg Film-coated Tablets  
Ibuprofen 400 mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives (M01A E01)</td>
</tr>
</tbody>
</table>
| Pharmaceutical form and strength(s)             | Film-coated tablets  
200 mg and 400 mg |
| Reference numbers for the Decentralised Procedure | UK/H/4780/001/DC  
UK/H/4780/002/DC |
| Reference Member State                          | UK                                                                            |
| Member States concerned                        | Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Sweden and Slovakia |
| Marketing Authorisation Number(s)               | PL 16028/0156  
PL 16028/0157 |
| Name and address of the authorisation holder     | Galpharm Healthcare Limited  
Hugh House  
Upper Cliffe Road  
Dodworth Business Park  
Dodworth  
South Yorkshire S75 3SP  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Ibuprofen

rINN: Ibuprofen
Chemical name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid
Structure:

![Chemical Structure of Ibuprofen]

Molecular formula: C_{13}H_{18}O_{2}
Molecular weight: 206.3
Appearance: White or almost white crystalline powder or colourless crystals
Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates

All aspects of the manufacture and control of the active substance ibuprofen from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, as follows:

Tablet core:
For the 200 mg Film-coated Tablets: hypromellose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycolate (Type A), colloidal anhydrous silica
For the 400 mg Film-coated Tablets: croscarmellose sodium, lactose monohydrate, magnesium stearate, maize starch, povidone, colloidal anhydrous silica, talc

Film-coating:
Opadry-II White 85F18422 comprising macrogol 3350, poly(vinyl-alcohol), talc, titanium dioxide

With the exception of the Opadry-II White film-coating agent, all excipients used comply with their respective European Pharmacopoeia monographs. Opadry-II White film-coating complies with a suitable in-house specification, however, its individual constituents comply with their respective European Pharmacopoeia monographs.

With the exception of the lactose monohydrate, none of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the currently licensed products, Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB).
A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of each strength of finished product. The results are satisfactory.

**Finished Product Specification**
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is packaged in aluminium/polyvinylchloride (PVC) blister packs. Blisters are packaged in an outer cardboard carton in pack sizes of 6, 8, 10, 12, 16, 20, 24, 30, 48, 50, 96 and 100 tablets.

The Marketing Authorisation Holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with the special storage conditions of “Do not store above 25°C” and “Keep in the original container in order to protect from light and moisture”.

**Bioequivalence/bioavailability**
A bioequivalence study was performed for each strength of product, which compared the pharmacokinetics of the test products Ibuprofen 200 mg and 400 mg Film-coated Tablets to those of the reference products Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PILs and text versions of the labels are acceptable from a pharmaceutical perspective.

The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Ibuprofen 200mg sugar-coated tablets (PL 16028/0013; Galpharm Healthcare Limited) was provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains. As the PILs for Ibuprofen 200 mg and 400 mg Film-coated Tablets are consistent with the approved PIL for Ibuprofen 200mg sugar-coated tablets (PL 16028/0013) in their content and layout, additional readability testing is not deemed necessary.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.

### III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

**Study 1 - Ibuprofen 200 mg and 400 mg Sugar-Coated Tablets**
As part of work to register the currently authorised sugar-coated formulations of the products (PL 16028/0028 and PL 16028/0040) in Poland, a bioequivalence study was conducted to compare the pharmacokinetics of these products to those of the Polish reference product, as follows:

A balanced, open-label, randomised, three-treatment, six-sequence, three-period, single dose, three way crossover study comparing the pharmacokinetics of the test products Ibuprofen 400 mg Sugar-Coated Tablets (PL 16028/0040; Galpharm Healthcare Limited) and Ibuprofen 200 mg Sugar-Coated Tablets (PL 16028/0028; Galpharm Healthcare Limited) to those of the reference product Nurofen 200 mg Sugar-coated Tablets (Reckitt Benckiser Healthcare Sp.z.o.o., Poland) in healthy adult human subjects, under fasting conditions

Volunteers were given each treatment (1 x 400 mg tablet or 2 x 200 mg tablets) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 5 days.

A summary of the main pharmacokinetic results is presented in the table below:
Compared with the reference product, the 90% confidence intervals for the test products are within 80.00-125.00% for Cmax and AUC. It was concluded that ibuprofen 400 mg and 200 mg Sugar-coated Tablets are, therefore, bioequivalent with Nurofen 200 mg Sugar-coated Tablets.

The applicant requested a biowaiver to extrapolate the results of this bioequivalence study for sugar-coated tablets to the current applications for film-coated tablets. In support of this biowaiver request, comparative dissolution studies to demonstrate that the sugar-coated and film-coated products dissolve at similar rates were provided. However, as the dissolution studies did not adequately demonstrate equivalence between the sugar-coated and film-coated formulations for both strengths of product at each pH tested, the applicant was requested to submit further formal comparative bioequivalence studies between film-coated formulations of test and reference product. The following studies were, therefore, submitted:

Study 2 - Ibuprofen 200 mg Film-coated Tablets

A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Ibuprofen 200 mg Film-coated Tablets to those of the reference product Brufen 200 mg film-coated tablets (Abbott Scandinavia AB) in healthy adult human subjects, under fasting conditions.

Volunteers were given each treatment (a single dose of two 200 mg tablets) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 4 days.

A summary of the main pharmacokinetic results is presented in the table below:

### Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TestGeoLSM (T)</th>
<th>GeoLSM (R)</th>
<th>*T/R (%)</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cmax (μg/ml)</td>
<td>34.3642</td>
<td>35.0285</td>
<td>98.10</td>
<td>88.62-108.60</td>
</tr>
</tbody>
</table>
| AUC_{0-4} (hr.μg/ml)   | 111.6666       | 114.9646   | 97.13    | 94.37-99.97
Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00% for $C_{\text{max}}$ and AUC. Ibuprofen 200 mg Film-coated Tablets are, therefore, considered bioequivalent with Brufen 200 mg tablets.

Study 2 - Ibuprofen 400 mg Film-coated Tablets

A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Ibuprofen 400 mg Film-coated Tablets to those of the reference product Brufen 400 mg film-coated tablets (Abbott Scandanavia AB) in healthy adult human subjects, under fasting conditions.

Volunteers were given each treatment (a single dose of one 400 mg tablet) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 4 days.

A summary of the main pharmacokinetic results is presented in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_\tau$ $\mu$g/ml/h</th>
<th>$C_{\text{max}}$ $\mu$g/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$T_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>109.79</td>
<td>29.99</td>
<td>1.50</td>
<td>2.10</td>
</tr>
<tr>
<td>Reference</td>
<td>107.01</td>
<td>30.55</td>
<td>1.52</td>
<td>2.05</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>102.60 (99.67-105.62)</td>
<td>98.20 (91.94-104.87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\text{AUC}_\tau$ 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 (median)

$T_{1/2}$ half-life

*ln-transformed values

Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00% for $C_{\text{max}}$ and AUC. Ibuprofen 400 mg Film-coated Tablets are, therefore, considered bioequivalent with Brufen 400 mg tablets.

Efficacy

No new data on efficacy have been submitted and none are required for this type of application.

Safety

With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL and Labels

The SmPCs, PILs and text versions of the labels are acceptable from a clinical perspective.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

Suitable justification has been provided for not submitting a risk management plan for these products.
Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ibuprofen 200 mg and 400 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s products and the reference products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and text versions of labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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