Public Assessment Report

Decentralised Procedure

Ibuprofen 200 mg film-coated tablets
Ibuprofen 400 mg film-coated tablets
Ibuprofen 600 mg film-coated tablets

(Ibuprofen)

Procedure No: UK/H/5989/001-003/DC

UK Licence Number: PL 20075/0435-0437

Accord Healthcare Limited.
LAY SUMMARY

Ibuprofen 200 mg, 400 mg and 600 mg film-coated tablets
(ibuprofen, film-coated tablet, 200 mg, 400 mg and 600 mg)

This is a summary of the Public Assessment Report (PAR) for Ibuprofen 200 mg, 400 mg and 600 mg film-coated tablets (PL 20075/0435-0437; UK/H/5989/001-003/DC). It explains how Ibuprofen 200 mg, 400 mg and 600 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, 400 mg and 600 mg film-coated tablets.

The products will be collectively referred to as Ibuprofen tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Ibuprofen tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ibuprofen tablets and what are they used for?
Ibuprofen tablets are ‘generic medicines’. This means that Ibuprofen tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden).

**Ibuprofen 200 mg film-coated tablets are used:**
- In adults and children over 6 years (>20 kg) for the short term treatment of fever and pain of mild to moderate intensity, including dysmenorrhea.
- For long term symptomatic treatment of pain and inflammation in chronic inflammatory rheumatic diseases.

**Ibuprofen 400 mg film-coated tablets are used:**
- In adults and children over 12 years (>40 kg) for the short term treatment of fever and pain of mild to moderate intensity, including dysmenorrhea.
- For long term symptomatic treatment of pain and inflammation in chronic inflammatory rheumatic diseases.

**Ibuprofen 600 mg film-coated tablets** can be used in symptomatic treatment of pain and inflammation in rheumatoid arthritis (including systemic Juvenile Idiopathic Arthritis [sJIA]), osteoarthritis, seronegative arthropathies and in painful swelling and inflammation after soft tissue injuries.

How do Ibuprofen tablets work?
Ibuprofen tablets belong to a group of medicines called NSAIDs (non-steroidal anti-inflammatory drugs). They reduce fever, relieve pain and have an anti-inflammatory effect.

How are Ibuprofen tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient must always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

Ibuprofen tablets should be taken with or after food, with plenty of fluid. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat
irritation.
The recommended dose of this medicine will depend on the patient’s age, weight and the reason why they have been prescribed this medicine.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Ibuprofen tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Ibuprofen tablets have been shown in studies?**
Because Ibuprofen tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Ibuprofen tablets?**
Because Ibuprofen tablets are generic medicines and are bioequivalent to the reference medicines Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden), their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflets.

For the full list of all side effects reported with Ibuprofen tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Ibuprofen tablets approved?**
It was concluded that, in accordance with EU requirements, Ibuprofen tablets have been shown to have comparable quality and to be bioequivalent to Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden). Therefore, the MHRA decided that, as for Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden); the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Ibuprofen tablets?**
A risk management plan (RMP) has been developed to ensure that Ibuprofen tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Ibuprofen tablets 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/healthcare professionals will be monitored/reviewed continuously.

**Other information about Ibuprofen tablets**
For Ibuprofen 200 mg film-coated tablets (PL 20075/0435; UK/H/5989/001/DC):
Bulgaria, Estonia, France, Ireland, Malta, the Netherlands, Sweden and the UK agreed to grant Marketing Authorisations for Ibuprofen tablets on 04 July 2016. Marketing Authorisations were granted in the UK on 05 August 2016.
For Ibuprofen 400 mg film-coated tablets (PL 20075/0436; UK/H/5989/002/DC):
Austria, Bulgaria, Estonia, Finland, France, Ireland, Italy, Malta, the Netherlands, Sweden and the UK agreed to grant Marketing Authorisations for Ibuprofen tablets on 04 July 2016. Marketing Authorisations were granted in the UK on 05 August 2016.

For Ibuprofen 600 mg film-coated tablets (PL 20075/0437; UK/H/5989/003/DC):
Austria, Bulgaria, Estonia, Finland, Ireland, Italy, Malta, the Netherlands and the UK agreed to grant Marketing Authorisations for Ibuprofen tablets on 04 July 2016. Marketing Authorisations were granted in the UK on 05 August 2016.

The full PAR for Ibuprofen tablets follows this summary.

For more information about treatment with Ibuprofen tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.
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INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited, marketing authorisations for the medicinal products Ibuprofen tablets (PL 20075/0435-0437; UK/H/5989/001-003/DC). The products are prescription only medicines (POM).

Ibuprofen 200 mg film-coated tablets (PL 20075/0435; UK/H/5989/001/DC) are indicated:
- In adults and children over 6 years (>20 kg): Short term treatment of fever and pain of mild to moderate intensity, including dysmenorrhea.
- Long term symptomatic treatment of pain and inflammation in chronic inflammatory rheumatic diseases.

Ibuprofen 400 mg film-coated tablets (PL 20075/0436; UK/H/5989/002/DC) are indicated:
- In adults and children over 12 years (>40 kg): Short term treatment of fever and pain of mild to moderate intensity, including dysmenorrhea.
- Long term symptomatic treatment of pain and inflammation in chronic inflammatory rheumatic diseases.

Ibuprofen 600 mg film-coated tablets (PL 20075/0437; UK/H/5989/003/DC) are indicated:
- Symptomatic treatment of pain and inflammation in rheumatoid arthritis (including systemic Juvenile Idiopathic Arthritis [sJIA]), osteoarthritis, seronegative arthropathies and in painful swelling and inflammation after soft tissue injuries.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and:

For Ibuprofen 200 mg film-coated tablets (PL 20075/0435; UK/H/5989/001/DC):
Bulgaria, Estonia, France, Ireland, Malta, the Netherlands and Sweden as Concerned Member States (CMS).

For Ibuprofen 400 mg film-coated tablets (PL 20075/0436; UK/H/5989/002/DC):
Austria, Bulgaria, Estonia, Finland, France, Ireland, Italy, Malta, the Netherlands and Sweden as Concerned Member States (CMS).

For Ibuprofen 600 mg film-coated tablets (PL 20075/0437; UK/H/5989/003/DC):
Austria, Bulgaria, Estonia, Finland, Ireland, Italy, Malta and the Netherlands as Concerned Member States (CMS).

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden) which were first authorised in the Union to Abbott Scandinavia AB, Sweden on 14 March 1975 (200 mg tablet strength), 08 October 1975 (400 mg strength) and 12 March 1982 (600 mg strength).

Ibuprofen belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). It contains the propionic acid derivative p-isobutyl-hydrotropic acid. Ibuprofen has anti-inflammatory, analgesic and antipyretic effects. The anti-phlogistic effect is comparable with that of acetylsalicylic acid and indometacin. The pharmacological effect of ibuprofen is probably associated with its ability to inhibit prostaglandin synthesis. Ibuprofen prolongs bleeding time through reversible inhibition of platelet aggregation.
Two bioequivalence studies (conducted under fed and fasting conditions) were submitted to support these applications. The applicant has stated that the bioequivalence studies were conducted in accordance with the protocol and all requirements including the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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, assembly and batch release of these products.

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 manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 04 July 2016. After a subsequent national phase, licences were granted in the UK on 05 August 2016.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 200 mg, 400 mg or 600 mg ibuprofen, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:
Tablet core:
Lactose monohydrate, maize starch, croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose and magnesium stearate.

Tablet coating:
Hypromellose, triacetin, titanium dioxide (E171) and erythrosine aluminum lake (E127).

All strengths of the finished product are packed into polyvinyl chloride (PVC) - aluminium blisters or PVC/polyvinylidene chloride (PVD) - aluminium blisters in pack sizes of:

200mg tablet strength:
10, 12, 14, 20, 21, 24, 28, 30, 42, 48, 50, 84 or 100 film-coated tablets in a carton.

400mg tablet strength:
10, 12, 14, 20, 21, 24, 28, 30, 40, 42, 48, 50, 60, 84, 100 or 500 film-coated tablets in a carton.

600 mg tablet strength:
10, 14, 21, 28, 30, 40, 42, 50, 60, 84, 100 or 500 film-coated tablets in a carton.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Ibuprofen
Chemical name: 2-[4-(2-methylpropyl)phenyl] propanoic acid (IUPAC name)

Structure:

![Structure of Ibuprofen]

Molecular formula: C_{13}H_{18}O_{2}
Molecular weight: 206.3 g/mol
Description: 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

Ibuprofen is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ibuprofen, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3. **Medicinal Product**

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 200 mg, 400 mg or 600 mg ibuprofen per tablet, that are generic versions of the reference products Brufen 200 mg, 400 mg and 600 mg filmdragerade tabletter (Abbott Scandinavia AB, Sweden). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the tablet coating which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and has shown satisfactory results.

**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.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 **Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
NON-CLINICAL ASPECTS

INTRODUCTION

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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

PHARMACOLOGY

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

PHARMACOKINETICS

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

TOXICOLOGY

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

ECOTOXICITY/ENVIRONMENTAL RISK ASSESSMENT (ERA)

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

DISCUSSION ON THE NON-CLINICAL ASPECTS

There are no objections to the approval of these applications from a non-clinical viewpoint.

CLINICAL ASPECTS

INTRODUCTION

The clinical pharmacology of ibuprofen is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of ibuprofen.

Based on the data provided, Ibuprofen tablets can be considered bioequivalent to Brufen 200 mg, 400 mg and 600 mg film-draged tabletter (Abbott Scandinavia AB, Sweden).

PHARMACOKINETICS

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1

An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of the applicant’s test product Ibuprofen 400 mg film-coated tablets (Accord Healthcare Limited, UK) versus the reference product Brufen 400 mg Tablets (Abbott Laboratories Limited, UK) in healthy, adult, human subjects under fed conditions.

Subjects fasted for 10 hours and then received a high fat, high calorie vegetarian breakfast. After 30 minutes, subjects were administered a single oral dose (1 x 400 mg tablet) of the test or reference product with 240mL of water. No other fluid was allowed for one hour before or after drug administration. Subjects remained seated for 3 hours and fasted for 5 hours post dose.
Blood samples were collected for plasma levels before dosing and up to and including 16 hours after each administration. The washout period between the treatment phases was 4 days. The plasma levels of the two enantiomers of the parent compound, S (+) ibuprofen and R (-) ibuprofen were analysed. The formal acceptance of bioequivalence was based on the levels of the S-ibuprofen enantiomer. The pharmacokinetic results are presented below:

Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} median, range) for S-Ibuprofen 400mg:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} mcg•h/mL</th>
<th>AUC_{0-\infty} mcg•h/mL</th>
<th>C\text{max} mcg/mL</th>
<th>t\text{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Ibuprofen</td>
<td>81.699 ± 20.4994</td>
<td>82.921 ± 21.4632</td>
<td>20.130 ± 6.0878</td>
<td>2.250 (1.000-6.000)</td>
</tr>
<tr>
<td>Reference Brufen</td>
<td>80.325 ± 20.6444</td>
<td>81.709 ± 21.5219</td>
<td>19.035 ± 5.6813</td>
<td>2.250 (0.750-8.000)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)  
102.2 (99.69-104.87%)  
102.0 (99.49-104.56%)  
105.9 (96.93-115.66%)

AUC\text{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.  
AUC\text{0-\infty} Area under the plasma concentration curve extrapolated to infinite time.  
C\text{max} Maximum plasma concentration  
t\text{max} Time until C\text{max} is reached

*In-transformed values

Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} median, range) for R-Ibuprofen 400mg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} mcg•h/mL</th>
<th>AUC_{0-\infty} mcg•h/mL</th>
<th>C\text{max} mcg/mL</th>
<th>t\text{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Ibuprofen</td>
<td>45.291 ± 7.6718</td>
<td>45.726 ± 7.7333</td>
<td>13.601 ± 3.1353</td>
<td>2.000 (0.750-6.000)</td>
</tr>
<tr>
<td>Reference Brufen</td>
<td>44.341 ± 7.4014</td>
<td>44.759 ± 7.4808</td>
<td>12.872 ± 2.4378</td>
<td>2.250 (0.500-6.000)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)  
102.2 (96.00-108.73%)  
102.2 (96.00-108.77%)  
104.9 (97.38-112.99%)  

AUC\text{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.  
AUC\text{0-\infty} Area under the plasma concentration curve extrapolated to infinite time.  
C\text{max} Maximum plasma concentration  
t\text{max} Time until C\text{max} is reached

*In-transformed values

Conclusion  
The 90% confidence intervals of the test/reference ratio for AUC and C\text{max} values for S-ibuprofen and R-ibuprofen in the fed state for the 400 mg test product strength lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Ibuprofen 400 mg film-coated tablets (Accord Healthcare Limited, UK) is bioequivalent to the reference product Brufen 400 mg Tablets (Abbott Laboratories Limited, UK).
STUDY 2
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant’s test product Ibuprofen 600 mg film-coated tablets (Accord Healthcare Limited, UK) versus the reference product Brufen Forte 600 mg Tablets (Abbott S.A/N.V, Belgium) in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x 600 mg tablet) of either of the test products or the reference product in sitting posture with 240 mL of drinking water. Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 4 days. The plasma levels of the two enantiomers of the parent compound, S (+) ibuprofen and R (-) ibuprofen were analysed. The formal acceptance of bioequivalence was based on the levels of the S-ibuprofen enantiomer. The pharmacokinetic results are presented below:

Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> median, range) for S-Ibuprofen 600 mg:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Arithmetic Means (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt;</td>
<td>96.926 ± 25.8934</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt;</td>
<td>101.326 ± 29.4319</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>22.695 ± 4.0366</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2.000 (0.750 - 5.000)</td>
</tr>
</tbody>
</table>

1 Median (Min - Max)

Table: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> median, range) for R-Ibuprofen 600 mg:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Arithmetic Means (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt;</td>
<td>72.554 ± 18.8002</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt;</td>
<td>73.873 ± 19.5168</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>21.273 ± 4.4976</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2.000 (0.750 - 5.000)</td>
</tr>
</tbody>
</table>

1 Median (Min - Max)

Table: Bioequivalence Evaluation of S-Ibuprofen 600 mg

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Mean Ratio Test/Reference</th>
<th>90% Confidence Intervals</th>
<th>CV%&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt;</td>
<td>100.2</td>
<td>98.11 - 102.32</td>
<td>5.3</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt;</td>
<td>100.9</td>
<td>98.20 - 103.76</td>
<td>6.9</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>103.0</td>
<td>98.57 - 107.65</td>
<td>11.1</td>
</tr>
</tbody>
</table>

<sup>1</sup> Estimated from the Residual Mean Squares.

Table: Bioequivalence evaluation of R-Ibuprofen 600 mg:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Mean Ratio Test/Reference</th>
<th>90% Confidence Intervals</th>
<th>CV%&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt;</td>
<td>98.2</td>
<td>93.79-102.75</td>
<td>11.5</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt;</td>
<td>99.0</td>
<td>94.17-104.00</td>
<td>12.5</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>103.6</td>
<td>98.31-109.10</td>
<td>13.1</td>
</tr>
</tbody>
</table>

<sup>1</sup> Estimated from the Residual Mean Squares.
Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for S-ibuprofen and R-ibuprofen administered under fasting conditions for the 600 mg test product strength lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**)’. Thus, the data support the claim that the applicant’s test product Ibuprofen 600 mg film-coated tablets (Accord Healthcare Limited, UK) is bioequivalent to the reference product Brufen Forte 600 mg Tablets (Abbott S.A/N.V, Belgium).

As the 200 mg, 400 mg and 600 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 400mg and 600 mg tablet strengths can be extrapolated to the 200 mg strength tablets.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (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 ibuprofen.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Gastrointestinal perforation, ulceration and bleeding (PUB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature closure of the foetal ductus arteriosus (use during third trimester of pregnancy)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions in patients with previous hypersensitivity reactions to NSAIDs or aspirin</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm in patients with asthma or allergic disease</td>
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<tr>
<td></td>
<td>Arterial thrombotic events (MI and stroke) (at 2400mg/day)</td>
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<tr>
<td></td>
<td>Cardio-renal effects</td>
</tr>
<tr>
<td></td>
<td>Prolonged bleeding time/coagulation disorders</td>
</tr>
<tr>
<td></td>
<td>Serious skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis</td>
</tr>
<tr>
<td></td>
<td>Renal toxicity</td>
</tr>
<tr>
<td></td>
<td>Hepatic disorders</td>
</tr>
</tbody>
</table>

| Important potential risks | Foetal cardiac malformation, gastroschisis and miscarriage (use during early pregnancy) |

| Missing information | Use during breast feeding |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.
V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Solifenacin succinate 5/10mg film-coated tablets (Accord Healthcare Limited) and Brufen 200/400/600 mg film-coated tablets (Accord Healthcare Limited). The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Ibuprofen tablets is presented below: