Public Assessment Report

Decentralised Procedure

Abfen 600 mg Effervescent Granules

(Ibuprofen)

Procedure No: UK/H/5137/001/DC

UK Licence No: PL 46302/0008

Mylan Products Ltd
This is a summary of the Public Assessment Report (PAR) for Abfen 600 mg Effervescent Granules (UK/H/5137/001/DC; PL 46302/0008). It explains how Abfen 600 mg Effervescent Granules 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 Abfen 600 mg Effervescent Granules.

This medicinal product is referred to as Abfen Granules in the remainder of the lay summary for ease of reading.

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

**What are Abfen Granules and what are they used for?**

Abfen Granules are a ‘generic medicine’. This means that this product is similar to a ‘reference medicine’ already authorised in the UK called Brufen 600 mg Effervescent Granules (Abbott Laboratories Limited).

Abfen Granules are used:

- to relief of pain and inflammation in conditions such as osteoarthritis, rheumatoid arthritis, arthritis of the spine (ankylosing spondylitis), swollen joints, frozen shoulder, bursitis, tendinitis, tenosynovitis, lower back pain, sprains and strains.
- to treat other painful conditions such as toothache, pain after operations, period pain and headache, including migraine.

**How do Abfen Granules work?**

Abfen Granules contain the active substance, ibuprofen, which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). This medicine provides relief by changing the body’s response to pain and inflammation.

**How are Abfen Granules used?**

Abfen Granules are taken by mouth. One sachet must be poured into a small glass of water. Patients with sensitive stomach must take this medicine with or just after food.

The recommended dose for adults (18 years and older) is 1 sachet (600 mg) taken two or three times a day. A doctor may increase or decrease the dose depending on what patients are being treated for. Patients must not take more than 4 sachets (2,400 mg) in any 24 hours.

Abfen Granules are not recommended for children and adolescents under 18 years of age.

Patients with liver problem, kidney problem or the elderly (over 65 years) may be given the lowest dose possible by a doctor.

Abfen Granules are obtained on a prescription from a doctor.

For further information on how Abfen Granules are used, refer to the Summary of Product Characteristics or package leaflet available on the MHRA website.
How have Abfen Granules been studied?
Because Abfen Granules are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Brufen 600 mg Effervescent Granules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Why are Abfen Granules approved?
It was concluded that, in accordance with EU requirements, Abfen Granules have been shown to have comparable quality and to be bioequivalent to Brufen 600 mg Effervescent Granules. Therefore, the view was that, as for Brufen 600 mg Effervescent Granules the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Abfen Granules?
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

Other information about Abfen Granules
Bulgaria, Denmark, Estonia, Finland, Hungary, Ireland, Lithuania, Latvia, Norway, Romania, Slovenia and the UK agreed to grant a Marketing Authorisation for Ibuprofen 600mg Effervescent Granules on 11 April 2013. A Marketing Authorisation was granted in the UK on 09 May 2013.

A Marketing Authorisation was originally granted to Rocksring Healthcare Limited (PL 18866/0061) on 09 May 2013 with the name Ibuprofen 600mg Effervescent Granules. This licence underwent a change of ownership procedure to Abbot laboratories Limited (PL 00037/0667) on 16 October 2013. Following this change of ownership procedure the name of the product was changed from Ibuprofen 600mg Effervescent Granules to Abfen 600mg Effervescent Granules via a variation that was approved on 25 July 2014. The Marketing Authorisation underwent further changes of ownership to BGP products Limited (PL 43900/0008) on 25 February 2015 and then to the current Marketing Authorisation holder, Mylan Products Limited (PL 46302/0008), on 11 November 2016.

The full PAR for Abfen Granules follows this summary.

This summary was last updated in February 2017.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Ibuprofen 600 mg Effervescent Granules (PL 18866/0061; UK/H/5137/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Bulgaria, Denmark, Estonia, Finland, Hungary, Ireland, Lithuania, Latvia, Norway, Romania and Slovenia as Concerned Member States (CMS).

This product is a prescription-only medicine (legal classification POM).

This was an application 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 600 mg Effervescent Granules (Abbott Laboratories Limited), which was initially granted a marketing authorisation in the UK on 01 November 1990. The reference product used in the bioequivalence study was Brufen 600 mg Film-coated Tablets (Abbott Scandinavia AB, Sweden).

Ibuprofen 600 mg Effervescent Granules are indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies. In the treatment of non-articular rheumatic conditions the product is indicated in peri-articular conditions such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low back pain. It can also be used for soft-tissue injuries such as sprains and strains and in the relief of moderate pain such as dysmenorrhea, dental and post-operative pain and for symptomatic relief of headache including migraine headache.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. The pharmacological effects of ibuprofen are probably associated with its ability to inhibit prostaglandin synthesis, which it achieves by competitive inhibition of the two isomers of cyclooxygenase, COX-1 and COX-2.

No non-clinical studies were conducted, which is acceptable given that the application was 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 study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of Ibuprofen 600mg Effervescent Granules (the test product) versus Brufen 600mg Film-coated Tablets (the reference product). The bioequivalence study was 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 this product.

The RMS and CMS considered that the application could be approved with the end of procedure on 11 April 2013. After a subsequent national phase, a licence was granted in the UK on 09 May 2013.
A Marketing Authorisation was originally granted to Rockspring Healthcare Limited (PL 18866/0061) on 09 May 2013 with the name Ibuprofen 600mg Effervescent Granules. This licence underwent a change of ownership procedure to Abbot laboratories Limited (PL 00037/0667) on 16 October 2013. Following this change of ownership procedure the name of the product was changed from Ibuprofen 600mg Effervescent Granules to Abfen 600mg Effervescent Granules via a variation that was approved on 25 July 2014. The Marketing Authorisation underwent further changes of ownership to BGP products Limited (PL 43900/0008) on 25 February 2015 and then to the current Marketing Authorisation holder, Mylan Products Limited (PL 46302/0008), on 11 November 2016.
II Quality aspects

II.1 Introduction

Each sachet contains 600 mg of ibuprofen as an active substance. Abfen 600 mg Effervescent Granules are formulated as white granules with an orange flavour.

Other ingredients consist of the pharmaceutical excipients, namely croscarmellose sodium, microcrystalline cellulose, malic acid, saccharin sodium, sucrose, povidone, orange flavour, sodium laurilsulfate, sodium hydrogen carbonate and anhydrous sodium carbonate.

With the exception of the orange flavouring agent, which complies with a suitable in-house standard, all excipients comply with their respective European Pharmacopoeia monographs.

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 finished product is packaged in heat-sealed sachets consisting of a paper/polythene/aluminium foil/polythene laminate in pack sizes of 10, 20, 30, 40 and 50 sachets. 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.

II.2 Drug Substance

Ibuprofen

INN: Ibuprofen
Chemical Name: (±)-2-[(p-isobutylphenyl) propionic acid (2RS)-2-[4-(2 methylpropyl)phenyl]propanoic acid

Structure:

```
    CH3
   /   \
  /     \  \    \CH3
 C13H18O2
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Molecular formula: C_{13}H_{18}O_{2}
Molecular weight: 206.28 g/mol
Appearance: White or almost white crystalline powder or colourless crystals, which are practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride

Ibuprofen is the subject of a European Pharmacopoeia monograph.

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

Pharmaceutical development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the currently licensed product, Brufen 600 mg Effervescent Granules (Abbott Laboratories Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the proposed product and its respective reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, 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 production-scale batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on commercial-scale 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 3 years, with the storage conditions, “Do not store above 25°C. Store in the original package in order to protect from light and moisture”.

Bioequivalence/bioavailability
A bioequivalence study was performed, which compared the pharmacokinetics of Ibuprofen 600mg Effervescent Granules (test product) versus Brufen 600mg Film-coated tablets (reference product).

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III 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.
A suitable environmental risk assessment has been submitted and indicates that the use of the product does not pose an immediate risk to the environment.

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

**IV Clinical aspects**

**IV.1 Introduction**

The clinical pharmacology of ibuprofen is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

**IV.2 Pharmacokinetics**

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

**A randomised, single-dose, 4-way crossover bioequivalence study of Ibuprofen 600mg Effervescent Granules (test) and Brufen 600mg Film-coated Tablets (reference) in fed and fasting healthy male volunteers.**

Volunteers were given the treatment after a supervised 10 hour fast (or 30 minutes after a high-fat breakfast, when investigating food effect). Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 14 hours post-dose. Each regimen was separated by a 7-day washout period.

Treatments were as follows:
- Regimen A: Single dose of Ibuprofen 600mg Effervescent Granules (test), fasting
- Regimen B: Single dose of Ibuprofen 600mg Effervescent Granules (test), fed
- Regimen C: An additional marketed formulation of ibuprofen 600mg effervescent granules, fasting
- Regimen D: Single dose of Brufen 600mg Film-coated Tablets (reference), fasting

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Treatments were as follows:
- Regimen A: Single dose of Ibuprofen 600mg Effervescent Granules (test), fasting
- Regimen B: Single dose of Ibuprofen 600mg Effervescent Granules (test), fed
- Regimen C: An additional marketed formulation of ibuprofen 600mg effervescent granules, fasting
- Regimen D: Single dose of Brufen 600mg Film-coated Tablets (reference), fasting
IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for this type of application.

IV.5 Clinical safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 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 this product.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
A bridging report referring to 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 the product Brufen 400 mg Effervescent Granules (Abbott) 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.

VI Overall conclusion, benefit/risk assessment and recommendation
QUALITY
The important quality characteristics of Ibuprofen 600mg Effervescent Granules 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 product and the reference product Brufen 600mg Film-coated Tablets (Abbott Scandinavia AB).
No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

**BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. 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.
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website. The current approved UK labelling is presented below.

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS WITH SACHETS (10, 20, 30, 40, 50)

### 1. NAME OF THE MEDICINAL PRODUCT

Abfen 600 mg Effervescent Granules

Ibuprofen

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 600 mg ibuprofen.

### 3. LIST OF EXCIPIENTS

Also contains sucrose and sodium.
See leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Effervescent granules

10 sachets
20 sachets
30 sachets
40 sachets
50 sachets

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

-
8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan Products Ltd.
20 Station Close
Potters Bar
Herts
EN6 1TL
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 46302/0008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Empty the contents of the sachet into a glass of water of 125 ml; stir and drink as soon as fizzing stops.

16. INFORMATION IN BRAILLE

Abfen 600mg Effervescent Granules
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
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<tbody>
<tr>
<td>Abfen 600 mg Effervescent Granules</td>
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<tr>
<td>Ibuprofen</td>
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<tr>
<td>Oral use</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Empty the contents of the sachet into a glass of water of 125 ml; stir and drink as soon as fizzing stops.</td>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<tr>
<th>4. BATCH NUMBER</th>
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<tr>
<td>Lot:</td>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tbody>
<tr>
<td>Each sachet contains 600 mg ibuprofen.</td>
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<tr>
<th>6. OTHER</th>
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<tbody>
<tr>
<td>Also contains sucrose and sodium.</td>
</tr>
<tr>
<td>See leaflet for further information.</td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
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</tbody>
</table>
Table of content of the PAR update for MRP and DCP

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

The following table lists safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tr>
<td>16/11/2016</td>
<td>Type IB</td>
<td>To update SmPC fragments 4.2, 4.4, 4.8 and 5.1 in line with the reference product. Consequently, the patient information leaflet (PIL) has also been updated.</td>
<td>Approved on 15 January 2017</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 46302/0008 - 0004

Product: Abfen 600 mg Effervescent Granules

Marketing Authorisation Holder: Mylan Products Ltd

Active Ingredient: ibuprofen

Reason:
To update SmPC fragments 4.2, 4.4, 4.8 and 5.1 in line with the reference product. Consequently, the patient information leaflet (PIL) has also been updated.

Supporting evidence
The applicant has submitted updated sections of the SmPC and PIL.

Evaluation
The amended sections of the SmPC and PIL are satisfactory.

Conclusion
The updated SmPC fragments and PIL have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

Decision: Grant
Date: 15 January 2017