UK Public Assessment Report

Flarin 200 mg soft capsules
(ibuprofen)

UK Licence No: PL 42459/0002

Infirst Healthcare Limited
Lay Summary
Flarin 200 mg soft capsules
(ibuprofen)

This is a summary of the public assessment report (PAR) for Flarin 200 mg soft capsules. Flarin 200 mg soft capsules will be referred to as Flarin 200 mg capsules throughout this report, for ease of reading. It explains how Flarin 200 mg capsules 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 Flarin 200 mg capsules.

For practical information about using Flarin 200 mg capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Flarin 200 mg capsules and what are they used for?
This medicine is the same as Ibucaps Ibuprofen 200mg Soft Gelatin Capsules, which is already authorised. The company that makes Ibucaps Ibuprofen 200mg Soft Gelatin Capsules has agreed that this marketing authorisation can be used as a basis for the grant of an identical marketing authorisation for Flarin 200 mg capsules (informed consent).

Flarin 200 mg capsules are used for relief from rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia (sharp pain along nerves), migraine, headache, dental pain, period pain, feverishness, and cold and flu symptoms.

How do Flarin 200 mg capsules work?
This medicine contains ibuprofen, which belongs to a group of medicines called the non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen works as a painkiller by blocking the production of chemicals in the body called prostaglandins. Prostaglandins are substances released in response to illness or injury. They cause pain and swelling (inflammation). Prostaglandins that are released in the brain can also cause a high temperature (fever).

How are Flarin 200 mg capsules used?
The capsules should be swallowed whole with water.

The usual dose is one or two capsules (200 mg – 400 mg) up to three times a day, as required. The maximum dose is 400 mg and at least 4 hours should be left between doses. No more than 6 capsules should be taken in a 24 hour period.

This medicine is intended for short-term use only. Patients should take the lowest dose for the shortest time necessary to relieve their symptoms and should not take this medicine for longer than 10 days unless told to do so by a doctor.

The capsules can be obtained without a prescription.

How have Flarin 200 mg capsules been studied?
Flarin 200 mg capsules are considered to be identical to previously authorised Ibucaps Ibuprofen 200mg Soft Gelatin Capsules, with the same benefits and risks. Therefore, no new studies have been provided for Flarin 200 mg capsules but reference is made to the marketing authorisation for Ibucaps Ibuprofen 200mg Soft Gelatin Capsules.
What are the possible side effects of Flarin 200 mg capsules?
For the full list of all side effects reported with Flarin 200 mg capsules, see Section 4 of the PIL. For the full list of restrictions, see the PIL.

Why are Flarin 200 mg capsules approved?
The Medicines and Healthcare products Regulatory Agency (MHRA) decided that the benefits of Flarin 200 mg capsules are greater than their risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Flarin 200 mg capsules?
A Risk Management Plan has been developed to ensure Flarin 200 mg capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the PIL for Flarin 200 mg capsules, 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 and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Flarin 200 mg capsules
A marketing authorisation was granted in the UK on 15 September 2014.

This summary was last updated in March 2015.

The full PAR for Flarin 200 mg capsules follows this summary.
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I Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted in first HEALTHCARE Ltd a marketing authorisation for the medicinal product Flarin 200 mg capsules (PL 42459/0002) on 15 September 2014. Flarin 200 mg capsules were originally authorised as a General Sales List (GSL) medicine in pack sizes of 4, 10 and 16 capsules. The marketing authorisation was varied to add a pack size of 30 capsules and to change the legal supply status to Pharmacy (P).

Flarin 200 mg soft capsules are indicated for the relief of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, and symptoms of colds and influenza. Subsequent to the initial grant of this marketing authorisation an indication for the relief of pain of non-serious arthritic conditions was added via a variation.

This application was submitted as an abridged application, according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to the marketing authorisation for Ibucaps Ibuprofen 200mg Soft Gelatin Capsules (PL 14338/0001), which was granted to Banner Pharmacaps Europe B.V. on 28 April 2004.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

No new data were submitted nor were necessary for this simple application, as the data are identical to those provided for the previously authorised product.
II  Quality aspects

II.1  Introduction
This is an abridged application for Flarin 200 mg soft capsules, submitted under Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to Ibucaps Ibuprofen 200mg Soft Gelatin Capsules (PL 14338/0001). The current application is considered valid.

Expert reports are provided and are acceptable.

The name of the product and its appearance are essentially identical to that of the cross-reference product and are acceptable.

The capsules have the same strength, form and route of administration as the cross-reference product.

The product’s composition is identical to that of the cross-reference product and is acceptable.

With the exception of gelatin, none of the excipients are produced with materials of animal or human origin. Satisfactory declarations of compliance with current TSE/BSE regulations have been provided by all suppliers of the gelatin.

The capsules are stored in blister packs consisting of opaque, white 250 micron polyvinyl chloride (PVC)/30 micron polyethylene, coated with 90 g/m² polyvinylidene chloride (PVDC) and heat sealed to 30 micron aluminium foil. The blisters are packed into cardboard cartons. Package sizes of 4, 10, 16 or 30 capsules per carton have been authorised.

II.2  Drug Substance

Ibuprofen
The drug substance specification is identical to that of the reference product and is acceptable.

II.3  Medicinal Product

Pharmaceutical development
No bioequivalence data are required to support this simple abridged application because the product is identical to a product that is already authorised.

Manufacture of the product
The manufacturing sites are identical to those of the reference product and are acceptable.

The manufacturing process is identical to that of the reference product and is acceptable.

Product Specifications
The finished product specification is identical to that of the reference product and is acceptable.

Stability of the product
The proposed shelf-life and storage conditions of the finished product are identical to the reference product and are acceptable.
II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended for this application.

III Non-clinical aspects

As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

The marketing authorisation holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA).

The grant of a marketing authorisation is recommended.

IV Clinical aspects

As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The marketing authorisation holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan (RMP)
The marketing authorisation holder has submitted an 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 Flarin 200 mg capsules.

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

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hypersensitivity to NSAIDs or aspirin</th>
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<tbody>
<tr>
<td></td>
<td>Bronchospasm in patients with a history of bronchial asthma or allergic disease</td>
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<td></td>
<td>Gastrointestinal disorders - gastrointestinal bleeding</td>
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<td>Premature closure of the foetal ductus arteriosus</td>
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<td>Renal disorders</td>
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<td>Hepatic disorders</td>
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<td>Serious skin reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis)</td>
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<thead>
<tr>
<th>Important potential risks</th>
<th>Cardiovascular thrombotic events</th>
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<tbody>
<tr>
<td></td>
<td>Aseptic meningitis in patients with SLE and mixed connective tissue disease</td>
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<td>Impaired female fertility</td>
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<td>Off-label use in children aged &lt;12 years</td>
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<tr>
<th>Missing information</th>
<th>Use in pregnancy</th>
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<td>Use during breast-feeding</td>
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</table>
Planned risk minimisation activities

### Important identified risks

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
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<td><strong>Hypersensitivity to NSAIDs or aspirin</strong></td>
<td>Reference is made in SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects Reference is made in Package Leaflet sections: 2. Before you take Flarin 200 mg Soft Capsules</td>
<td>None proposed</td>
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<td><strong>Bronchospasm in patients with a history of bronchial asthma or allergic disease</strong></td>
<td>Reference is made in SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects Reference is made in Package Leaflet section: 4. Possible side effects</td>
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<td>4.8 Undesirable effects</td>
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<td>4.9 Overdose</td>
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<td>2. Before you take Flarin 200</td>
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<td>4.6 Pregnancy and lactation</td>
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<td></td>
<td>Reference about use of ibuprofen</td>
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**Important potential risks**

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<td><strong>Impaired female fertility</strong></td>
<td>Reference is made in SmPC section: 4.4 Special warnings and precautions for use Reference is made in Package Leaflet section: 2. Before you take Flarin 200</td>
<td>None proposed</td>
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</tbody>
</table>
Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
No PIL mock-ups were provided with this application and the applicant has not undertaken user consultation with target patient groups on the proposed PIL. Since the product is not to be marketed immediately, this is acceptable. The applicant is aware that the results of user testing or and/or a bridging report will be required for the PIL mock-up before marketing of the product.
VI Overall conclusion, benefit/risk assessment and recommendation

Quality
The data for this application are consistent with the data previously assessed for the marketing authorisation for Ibucaps Ibuprofen 200mg Soft Gelatin Capsules (PL 14338/0001) and, as such, have been judged to be satisfactory.

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

Efficacy
The product is identical to that previously licensed; therefore, no efficacy data are needed.

Safety
No new or unexpected safety concerns arose from this application.

Product literature
The content of the SmPC, PIL and labels are identical to those previously approved, apart from the necessary administrative updates to reflect the change in marketing authorisation.

Benefit/risk assessment
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the reference product. The benefit/risk balance 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 product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labels are listed below:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Flarin 200 mg soft capsules
Ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg ibuprofen.

3. LIST OF EXCIPIENTS

Also contains:
Ponceau 4R (E124) and sorbitol (see leaflet for more details).

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsules containing 200 mg ibuprofen.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not take if you:

- have or (have had two or more episodes of) stomach ulcer, perforation or bleeding
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers or aspirin with a daily dose above 75 mg.

Speak to a pharmacist or your doctor before taking if you:

- Have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver kidney or bowel problems.
- are a smoker
- are pregnant

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C and store in the original pack.

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

infirst HEALTHCARE Ltd.
Central Point
45 Beech Street
London
EC2Y

12. MARKETING AUTHORISATION NUMBER(S)

PL 42459/0002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.
15. INSTRUCTIONS ON USE

Adults, the elderly and children aged 12 years and older:

Take 1 or 2 capsules with water, then if necessary 1 or 2 capsules every 4 hours. Do not chew capsules.

Do not exceed 6 capsules in 24 hours.

Not suitable for children under 12 years.

16. INFORMATION IN BRAILLE

Flarin 200 mg soft capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Flarin 200 mg Soft Capsule
Ibuprofen

2. NAME OF THE MARKETING AUTHORISATION HOLDER

infirst HEALTHCARE Ltd.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. OTHER
### Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 September 2014</td>
<td>Type IB variation</td>
<td>To add a 30 capsule pack to the finished product.</td>
<td>Approved – 28/10/2014</td>
</tr>
<tr>
<td>26 September 2014</td>
<td>Reclassification Type IB variation</td>
<td>To change the legal status from GSL to Pharmacy.</td>
<td>Approved – 05/11/2014</td>
</tr>
<tr>
<td>26 September 2014</td>
<td>Type IB</td>
<td>To update sections 4.8 (Undesirable effects) and 6.5 (Nature and content of container) of the Summary of Product Characteristics (SmPC), in line with the Quality Review of Documents (QRD) template. No other changes have been approved with this variation.</td>
<td>Approved – 12/01/2015</td>
</tr>
<tr>
<td>10 October 2014</td>
<td>Type II</td>
<td>To update the indications of the product by adding ‘pain of non-serious arthritic conditions’ as a new indication. The licence legal status is being changed from GSL to P. Consequential changes are made to the SmPC, Patient Information Leaflet (PIL) and Carton.</td>
<td>Approved – 28/01/2015</td>
</tr>
</tbody>
</table>
Annex 1

Our Reference: PL 42459/0002, Application 0004
Product: Flarin capsules 200 mg
Marketing Authorisation Holder: Infirst Healthcare Limited
Active Ingredient(s): Ibuprofen.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To update sections 4.8 (Undesirable effects) and 6.5 (Nature and content of container) of the Summary of Product Characteristics (SmPC), in line with the Quality Review of Documents (QRD) template. No other changes have been approved with this variation.

Linked / Related Variation(s) or Case(s):
Not applicable

Supporting Evidence
Revised SmPC fragments have been provided.

Evaluation
The updated sections of the SmPC are in line with the latest QRD template and are satisfactory.

Conclusion
The amendments to the SmPC fragments can be approved.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the Medicines and Healthcare products Regulatory Agency website.

Decision - Approved on 12 January 2015.
Annex 2

Reference: PL 42459/0002, Application 0003
Product: Flarin 200 mg soft capsules
Marketing Authorisation Holder: Infirst Healthcare Limited
Active Ingredients: Ibuprofen

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To update the indications of the product by adding ‘pain of non-serious arthritic conditions’ as a new indication. The licence legal status is being changed from General Sales List (GSL) to Pharmacy (P). Consequential changes are made to sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) and 5.1 (Pharmacodynamic properties) of the SmPC, and the Patient Information Leaflet (PIL) and Carton.

Linked / Related Variation(s) or Case(s):
Not applicable

Supporting Evidence
The MAH has supplied a clinical overview justifying the changes, a present/proposed document and an appropriate application form, as well as the updated SmPC, label and leaflet.
Evaluation

The applicant referenced the following published studies in the clinical overview:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study objectives</th>
<th>Treatment groups</th>
<th>Duration</th>
</tr>
</thead>
</table>
| Bradley 1991       | Double-blind study comparing high-dose and low-dose ibuprofen and paracetamol in osteoarthritis of the knee | Ibuprofen 2400 mg/day (n=51)  
Ibuprofen 1200 mg/day (n=52)  
Paracetamol 4000 mg/day (n=51) | 4 weeks |
| Bradley 1992       |                                                                                 |                                                                                 |           |
| Schiff and Minic, 2004 | Meta-analysis of two double-blind studies comparing OTC doses of ibuprofen with naproxen in osteoarthritis of the knee | Ibuprofen 400 mg t.i.d. (n=149)  
Naproxen sodium 660 mg (or 440 mg if ≥ 65 years) (n=146)  
Placebo (n=149) | 7 days |
| Boureau 2004       | Double-blind comparison of single and multiple doses of ibuprofen and paracetamol in patients with knee or hip osteoarthritis | Ibuprofen 400 mg (n=111)  
Paracetamol 1000 mg (n=111) | Single dose / 14 days |
| Muller-Fassbender 1987 | Double-blind comparison of S-adenosylmethionine and ibuprofen in osteoarthritis of the knee, hip and spine. | S-adenosylmethionine 1200 mg/day (n=18)  
Ibuprofen 400 mg x3 (n=18) | 4 weeks |
| Muller-Fassbender 1994 | Double-blind comparison of Glucosamine sulfate and ibuprofen in osteoarthritis of the knee. | Glucosamine sulfate 500 mg t.i.d. (n=100)  
Ibuprofen 400 mg t.i.d. (1200 mg/day) (n=99) | 4 weeks |

The studies all show that ibuprofen is efficacious in non-serious arthritis, with the doses presented showing efficacy.

Conclusion

The amendments to the SmPC fragments and PIL can be approved.

Other changes to the SmPC and PIL are currently being assessed in a parallel, pending Variation. As a consequence, the consolidated changes to the SmPC and PIL are not approved with this Variation.

In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for a product granted a marketing authorisation at a national level are available on the Medicines and Healthcare products Regulatory Agency website.

Decision - Approved on 28 January 2015.