Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Ibuprofen 400 mg soft capsules

(Ibuprofen)

PL 10321/0212

Resolution Chemicals Ltd

LAY SUMMARY

Ibuprofen 400 mg soft capsules
(Ibuprofen)

This is a summary of the Public Assessment Report (PAR) for Ibuprofen 400 mg soft capsules. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Ibuprofen soft capsules in this lay summary for ease of reading.

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

What are Ibuprofen soft capsules and what are they used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK) and the European Union (EU) called Nurofen Express 400 mg liquid capsules.

Ibuprofen soft capsules are used to
- relieve pain and inflammation in conditions such as osteoarthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), arthritis of the spine, ankylosing spondylitis, swollen joints, frozen shoulder, bursitis, tendinitis, tenosynovitis, lower back pain, sprains and strains.
- treat other painful conditions such as toothache, pain after operations, period pain and headache (including migraine).

How do Ibuprofen soft capsules work?
The active substance, ibuprofen, belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

How are Ibuprofen soft capsules used?
The pharmaceutical form of this medicine is soft capsules and the route of administration is oral (taken by mouth).

How to take the capsules
The patient should take their capsules with or after food and swallow the capsules whole with a glass of water. They should not chew, suck or burst the capsules.

Adults and children over 12 years
The daily dose is 600 mg to 1800 mg spread throughout the day. The patient’s doctor may choose to increase this dose depending on what the patient is being treated for; but no more than 2400 mg should be taken in one day.

Children
The usual daily dose is 20 mg per kg of their bodyweight each day, given in divided doses. The capsules should NOT be taken by children weighing less than 7 kg.

In cases of severe juvenile rheumatoid arthritis, the patient's doctor may increase the dose up to 40 mg per kg of bodyweight in divided doses.

The patient should avoid excessive use of painkillers. If the patient usually takes painkillers, especially combinations of different painkillers, they may damage their kidneys. **The patient should tell their doctor if they are already taking another painkiller before taking this medicine and the doctor will decide whether their patient should take this medicine.** This risk may be increased if the patient is dehydrated.

The use of painkillers for a long period of time has, in some patients, been linked to headaches, a condition called 'medication overuse headache'. Patients who have frequent or daily headaches despite (or because of) the regular use of pain killers should not be treated with increased doses of ibuprofen. The patient should tell their doctor if they have been having headaches while taking this medicine.

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

This medicine can only be obtained with a prescription.

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

What benefits of Ibuprofen soft capsules have been shown in studies?
Because Ibuprofen soft capsules are a generic medicine, studies in healthy volunteers have been limited to tests to determine that this medicine is bioequivalent to the reference medicine. 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 soft capsules?
Because Ibuprofen soft capsules are a generic medicine and are bioequivalent to the reference medicine, their benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the SmPC available on the MHRA website.

Why were Ibuprofen soft capsules approved?
It was concluded that, in accordance with EU requirements, Ibuprofen soft capsules have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ibuprofen soft capsules?
A Risk Management Plan (RMP) has been developed to ensure that Ibuprofen soft capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Ibuprofen soft capsules

A Marketing Authorisation for Ibuprofen soft capsules was granted in the UK on 04 March 2021.

The full PAR for Ibuprofen soft capsules follows this summary.

This summary was last updated in May 2021.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Ibuprofen 400 mg soft capsules (PL 10321/0212) could be approved.

The product is approved for the following indications:

- Ibuprofen soft capsules are indicated for analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's Disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.
- In the treatment of non-articular rheumatic conditions, Ibuprofen soft capsules are indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain; they can also be used in soft- tissue injuries such as sprains and strains.
- Ibuprofen soft capsules are also indicated for their analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for the symptomatic relief of headache including migraine headache.

Ibuprofen, the active substance is a non-steroidal anti-inflammatory drug (NSAID), with analgesic, antipyretic and anti-inflammatory action. The drug's therapeutic effects as an NSAID is thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended (Regulation 51B of The Human Medicines Regulation 2012, as amended), as a generic medicine of a suitable originator medicinal product, Nurofen Express 400 mg liquid capsules, that has been licensed within the United Kingdom (UK) and the European Union (EU) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference 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 is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing Authorisation was granted for this product on 03 March 2021.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 400 mg of ibuprofen in each soft capsule.

In addition to ibuprofen, this product also contains the excipients macrogol 600, potassium hydroxide and triglycerides, medium chain in the capsule fill. The capsule shell contains gelatine and sorbitol liquid. The capsule printing ink contains purified water; black iron oxide, isopropyl alcohol, propylene glycol and hypromellose.

The finished product is packaged in white opaque polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters in cartons of 60, 84, 100, 250 and 500 soft capsules. Not all pack sizes may be marketed.

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.

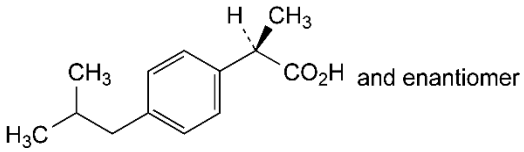
II.2 ACTIVE SUBSTANCE

rINN: Ibuprofen

Name: (2*RS*)-2-[4-(2-Methylpropyl)phenyl]propanoic acid

Molecular Formula: $C_{13}H_{18}O_2$

Chemical Structure:



Molecular Weight: 206.3 g/mol

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. Ibuprofen 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatine, no excipients of animal or human origin are used in the final product. The suppliers of gelatine has provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is

manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, is acceptable.

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
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of ibuprofen is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

Bioequivalence study (single-dose, fasting)

This study was an open-label, randomised, single-dose, two-treatment, two-period, two-sequence, crossover, oral bioequivalence study comparing the test product Ibuprofen Soft Gelatine Capsule 400 mg versus the reference product Nurofen Express 400 mg Liquid Capsule in normal, healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 400 mg capsule) of either treatment with approximately 240 ml of water. Blood samples were taken pre-dose and up to 12 hours post dose, with a washout period of eight days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Pharmacokinetic parameters for ibuprofen

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml
Test	116.42 ± 27.65	118.99 ± 29.39	45.24 ± 10.23
Reference	115.66 ± 27.10	117.64 ± 28.28	46.00 ± 9.56
***Ratio (90% CI)**	100.55 (**97.14 – 104.08**)	100.96 (97.45 – 104.61)	98.10 (**92.05 – 104.55**)

AUC_{0-t} = Area under the plasma concentration curve from administration to last observed concentration at time t

$AUC_{0-\infty}$ = Area under the plasma concentration curve extrapolated to infinite time

C_{max} = Maximum plasma concentration

*ln-transformed values

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended (Regulation 182(2) of The Human Medicines Regulations 2012, as amended). The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

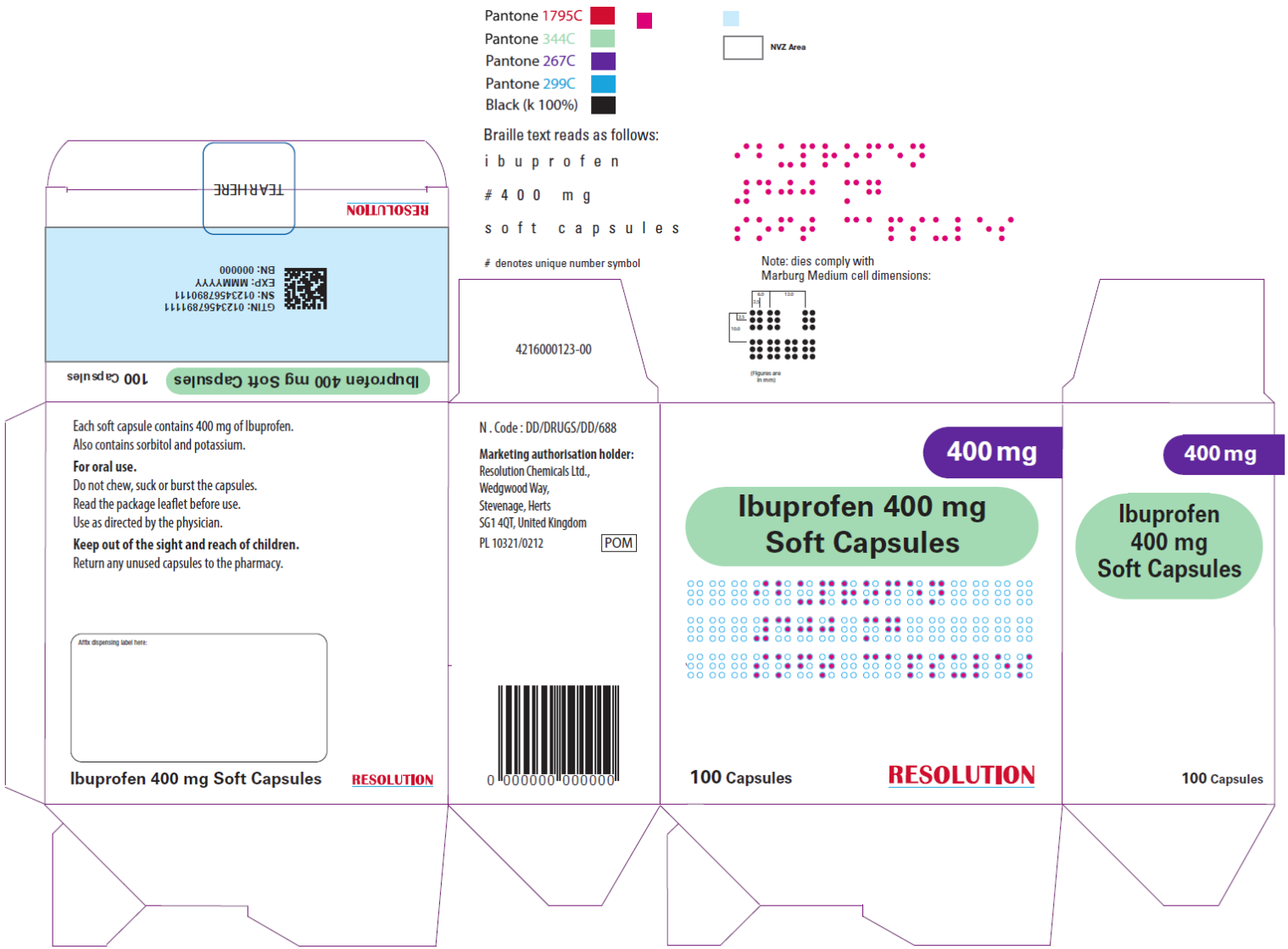
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines.

In accordance with Directive 2010/84/EU (Regulation 203 of The Human Medicines Regulations 2012, as amended), the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.



Please use manufacturers original profile for final compilation and print.

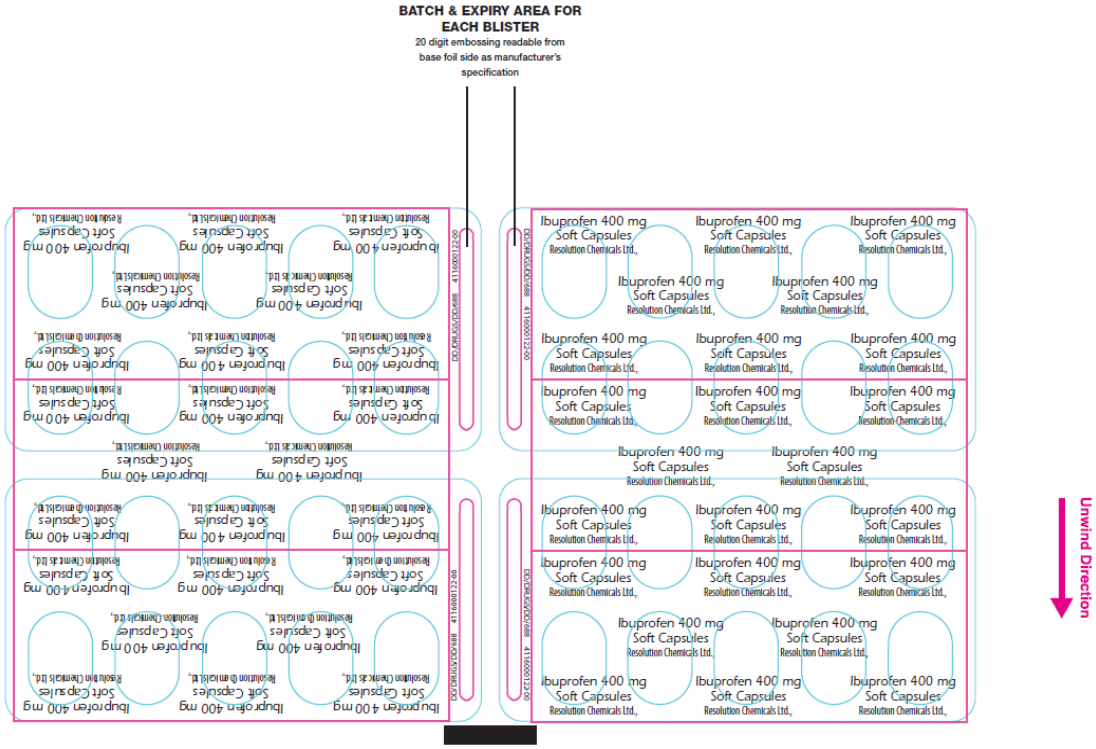

BATCH & EXPIRY AREA FOR EACH BLISTER
20 digit embossing readable from base foil side as manufacturer's specification
Ibuprofen 400 mg Soft Capsules Resolution Chemicals Ltd.,
Unwind Direction

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**