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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Nurofen Express 200mg & Nurofen Express Maximum Strength 400mg Coated Tablets

Ibuprofen as Ibuprofen Sodium Dihydrate

PA0979/032/010-011

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Nurofen Express 200mg tablets and Nurofen Express Maximum Strength 400mg tablets, from Reckitt Benckiser on 27th May 2011 for the relief of pain, such as is associated with headache, dental pain, fever, period pain, muscular strain, backache and for the management of the symptoms of cold and influenza.

This Article 8(3) application for Nurofen Express and Nurofen Express Maximum Strength was submitted as a new national application as a legal basis line extension to the various other Nurofen preparations already available.

The product is available over the counter in pharmacies.

Name of the product	Nurofen Express 200 mg, Express Maximum Strength 400 mg Tablets
Name(s) of the active substance(s) (INN)	Ibuprofen as Ibuprofen Sodium Dihydrate
Pharmacotherapeutic classification (ATC code)	M01A E01
Pharmaceutical form and strength(s)	Coated tablet, 200mg, 400mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0979/032/010-11
Marketing Authorisation Holder	Reckitt Benckiser Ireland Ltd, Dublin

II QUALITY ASPECTS

II.1. Introduction

This application is for Nurofen Express 200 mg, Express Maximum Strength 400 mg Tablets.

II.2 Drug substance

The active substance is Ibuprofen, as sodium ibuprofen dihydrate, a new salt of the established active substance ibuprofen which itself is described in the European Pharmacopoeia. The drug substance is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current standards. Batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal product

P.1 Composition

Brief description of the dosage form

Name of active substance	**Quantity**	**Unit**
Ibuprofen as sodium ibuprofen dihydrate	200, 400	mg

Name of excipients
Croscarmellose Sodium (E648)
Xylitol (E967)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)
Colloidal anhydrous silica (E551)
Carmellose sodium (E466)
Talc (E553b)
Acacia spray dried (E414)
Sucrose
Titanium dioxide (E171)
Macrogol 6000 powder

Opacode S-1-9460HV Black containing:
- shellac (E 904)
- iron oxide red (E172)
- antifoam (DC 1510)
- N-butylalcohol
- industrial methylated spirit
- Purified water

Alternative black ink containing:
- shellac
- iron oxide black(E172)
- propylene glycol

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for a coated tablet, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in various blister packs. The blisters are packed into cardboard. Evidence has been provided that the packaging materials comply with Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging types have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Nurofen Express Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

Ibuprofen acid is a well-established, non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

Sodium Ibuprofen 256mg and 512mg tablets have been shown to be therapeutically equivalent to ibuprofen acid 200mg and 400mg tablets respectively. Therefore, no further non-clinical data are provided since the non-clinical data for the original formulation are still valid.

IV CLINICAL ASPECTS

IV.1 Introduction

The IMB has been assured that good clinical practice (GCP) standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Ibuprofen acid is well absorbed from the gastrointestinal tract. Ibuprofen acid is extensively bound to plasma proteins. Ibuprofen acid diffuses into the synovial fluid. Peak plasma concentration of ibuprofen occurs 1 – 2 hours after administration of ibuprofen acid.
The median peak plasma concentration after administration of Nurofen Express Maximum Strength tablets containing 400mg of sodium ibuprofen is achieved in approximately 35 minutes. A comparison of the 2 x 256mg (ibuprofen sodium) Nurofen Express tablets with 2 x 200mg (ibuprofen acid) Nurofen tablets showed that the median peak plasma concentration was achieved more than twice as fast for the sodium ibuprofen (35 minutes) compared to the ibuprofen acid tablets (90 minutes).

Ibuprofen acid is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

The elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

Bioequivalence

Pivotal study NL0405

This was an open-label, randomised, single dose, three way crossover study in 22 healthy fasted volunteers to compare the rate of absorption of 2 x Nurofen 200mg tablets (each containing 200mg ibuprofen acid) with two test formulations of ibuprofen tablets (2 x Test 1 containing 256mg sodium ibuprofen, equivalent to 200ng ibuprofen acid) and (2 x Test 2 containing ibuprofen / poloxamer 407, containing 200mg ibuprofen free acid and 60mg poloxamer 407).

The pharmacokinetic parameters are provided in the tables below:

	Nurofen 2x200mg	Ibuprofen Sodium 2x256mg	Ibuprofen poloxamer 2x260 mg
Geometric means			
C_{max} (ug/ml)	31.88	41.47	35.22
AUC_T (h.ug/ml)	115.28	117.73	120.55
AUC_I (h.ug/ml)	117.71	119.73	122.75
T_{max} (h)	90	35	75

Ratio Test/Reference			90% Confidence Interval	
	Sodium Ibuprofen/ Nurofen	Poloxamer/ Nurofen	Sodium Ibuprofen/ Nurofen	Poloxamer/ Nurofen
C_{max}	130.06	110.48	118.86 – 142.32	100.96 - 120.89
AUC_T	0.97629	104.57	98.08 -106.44	100.38 - .93
AUC_I	0.97431	104.28	97.62 – 105.98	100.08 - `08.66

The data from this study indicates that sodium ibuprofen tablets and ibuprofen acid tablets have similar extents of absorption of ibuprofen, with 90% CI for AUC within the 0.8 – 1.25 equivalence range, as specified in the EU guidelines.
The rate of absorption of sodium ibuprofen was significantly faster than ibuprofen acid tablets, resulting in a significantly higher C_{max} after sodium ibuprofen, than ibuprofen acid tablets.

In addition to the above mentioned pivotal study, data from 6 supportive studies were supplied in the application.

Study AH-95-93 (NU5003)

This was an open-label, randomised, single dose, four-way crossover study in 16 healthy fasted volunteers to compare the rate of ibuprofen absorption of four ibuprofen products: Nurofen 200mg tablets, Dolormin (lysine ibuprofen tablets), an earlier formulation of sodium ibuprofen tablets and film coated 200mg ibuprofen tablets.

This study showed that ibuprofen from sodium ibuprofen tablets was absorbed significantly faster than that of standard Nurofen (ibuprofen acid) tablets although the two were bioequivalent in terms of C_{max} and AUC. Film coated ibuprofen acid tablets were bioequivalent to standard Nurofen (ibuprofen acid) tablets. Sodium ibuprofen tablets and film coated ibuprofen acid tablets were bioequivalent to lysine ibuprofen tablets.

Study NU5005

This was an open-label, randomised, single dose, three way crossover study in 15 healthy fasted volunteers comparing the absorption of three 200mg ibuprofen products: sodium ibuprofen, meglumine ibuprofen and lysine ibuprofen tablets.
This study showed that sodium ibuprofen and meglumine ibuprofen were both equivalent to lysine ibuprofen in terms of C_{max} and AUC, but not in terms of t_{max} which was significantly greater for sodium ibuprofen and meglumine ibuprofen.

Study NL9709

This was an open-label, randomised, single dose, three way crossover study in 24 healthy fasted volunteers to compare the absorption of 400mg doses of three ibuprofen products: Nurofen (ibuprofen acid) tablets, Dolormin (lysine ibuprofen) and an earlier formulation of sodium ibuprofen.
This study showed that Dolormin and sodium ibuprofen tablets were both bioequivalent to standard Nurofen tablets in terms of the extent, but not rate of absorption. The rate of absorption of ibuprofen from sodium ibuprofen and Dolormin was significantly faster than that from standard Nurofen.

Study NL0304

This was an open-label, single dose, randomised, five-way crossover study in 15 healthy fasted volunteers to compare the absorption of four formulations of 400mg sodium ibuprofen tablet, each with a different coat and an ibuprofen acid tablet incorporating sodium bicarbonate.

The results of this study showed that none of the formulations differed significantly in terms of AUC or t_{max} although the formulation including ibuprofen with sodium bicarbonate showed a trend for more rapid absorption than the standard sugar coated formulation.

Sorgel 2005 Pharmacokinetic Study 1

This was an open-label, randomised, single dose, five-way, crossover study in healthy fasted volunteers to compare the absorption from three tablet formulations (sodium ibuprofen, ibuprofen acid and lysine ibuprofen) and ibuprofen liquagels.
The results of this study showed that there were no significant differences in total extent of absorption between the formulations. The t_{max} was significantly shorter and the C_{max} was significantly higher for the sodium ibuprofen, lysine ibuprofen and ibuprofen liquigels compared with the standard Nurofen (ibuprofen acid) tablets. No significant differences were observed between the sodium ibuprofen, lysine ibuprofen and ibuprofen liquigels formulations.

Conclusions on bioequivalence

The results of the bioequivalence studies have shown that sodium ibuprofen 200mg tablets are bioequivalent to standard ibuprofen acid 200mg tablets with regard to the extent of absorption. The higher C_{max} achieved by sodium ibuprofen is within the therapeutic range for ibuprofen and is consistent with that for formulations of ibuprofen lysine which are marketed in some EU countries.

IV.3 Pharmacodynamics

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Sodium ibuprofen is the sodium salt of ibuprofen, a propionic acid derivative having analgesic, anti-inflammatory and anti-pyretic activity. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Following oral administration, sodium ibuprofen dissociates to ibuprofen acid and sodium. Sodium has no additional pharmacological activity and so therefore the pharmacological properties of sodium ibuprofen are the same as those of ibuprofen acid.

IV.4 Clinical Efficacy

To demonstrate the clinical efficacy of sodium ibuprofen the applicant has submitted a single clinical efficacy study.

Study NL0406

This was a double blind, parallel group, placebo controlled, randomised, single dose, two centre study, to compare the efficacy and onset of action of sodium ibuprofen tablets with that of another investigative ibuprofen formulation (ibuprofen/poloxmer), paracetamol and placebo in postoperative adult dental pain.

The results of the clinical study demonstrate that ibuprofen is effective in alleviating postoperative dental pain and that both ibuprofen formulations were significantly different from placebo in terms of time to first confirmed perceptible pain relief. Although a significantly greater proportion of subjects reported relief in the two ibuprofen groups compared with those in the paracetamol group, the divergence in onset times was only apparent from 45 minutes post dose onwards.

IV.5 Clinical Safety

Equivalence in terms of the total extent of absorption has been demonstrated between Nurofen Express (sodium ibuprofen) 256mg tablets and Nurofen (ibuprofen acid) 200mg tablets. Therefore the safety profile of sodium ibuprofen tablets would be expected to be the same as that for the currently authorised product Nurofen (ibuprofen acid) 200mg tablets. The warnings, precautions and adverse events included in the SmPC are the same.

Safety data are also available from the pivotal pharmacokinetic study NL0405, the clinical efficacy study, NL0406 and an endoscopy study NL9609. Safety data is also included for other formulations of sodium ibuprofen.

A post marketing safety review of ibuprofen sodium compared to ibuprofen acid and ibuprofen lysine has also been provided.

The safety profile of sodium ibuprofen is similar to that for ibuprofen lysine which is already licensed in some EU countries.

The safety profile of ibuprofen is well known and no further data are required.

The applicant does not propose to submit a separate Risk Management Plan for this product and this is accepted. Ibuprofen and its salts are a long established active with a well documented history. Consequently, the risk associated with the product is low and the Pharmacovigilance System as described in the dossier will adequately address any anticipated risks for the product.

The schedule for Periodic Safety Update Reports (PSUR) submission should be on a 3 yearly basis with the data lock point (DLP) 28th February 2011, in line with the Heads of Medicines Agencies (HMA) International Birth Date (IBD).

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ibuprofen is a well-established, non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

Sodium Ibuprofen 256mg and 512mg tablets have been shown to be therapeutically equivalent to Nurofen (ibuprofen acid) 200 mg and 400mg tablets respectively.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted, considered that Nurofen Express 200mg tablets and Nurofen Express Maximum Strength 400mg tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI REVISION DATE

May 2011