

IBUPROFEN 200MG TABLETS

PL 36263/0002

UKPAR

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IBUPROFEN 200MG TABLETS PL 36263/0002

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted MJK Consultancy Limited a Marketing Authorisation for the medicinal product Ibuprofen 200mg Tablets (PL 36263/0002) on 28 September 2011. Ibuprofen 200mg Tablets is a General Sales Licence (GSL) medicine.

Ibuprofen 200mg Tablets are indicated for the relief of pain, such as headache, migraine, dental pain, menstrual pain, rheumatic or muscular pain, and to reduce fever.

Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). These provide relief by changing the way the body responds to pain and high temperature.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ibuprofen 200mg Tablets outweigh the risks; hence Marketing Authorisation was granted.

**IBUPROFEN 200MG TABLETS
PL 36263/0002**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted MJK Consultancy Limited a Marketing Authorisation for the medicinal product Ibuprofen 200mg Tablets (PL 36263/0002) on 28 September 2011.

Ibuprofen 200mg Tablets is a General Sales Licence (GSL) medicine and is indicated for rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, period pain, feverishness, symptoms of colds and influenza.

This application was submitted under Article 10.3 of Directive 2001/83/EC, as a hybrid application. The reference product for this application is Nurofen 200mg tablets (Reckitt Benckiser Healthcare B.V., The Netherlands), which was first authorised in the Netherlands on 24 January 1985. The corresponding reference product in the UK is Nurofen 200mg tablets (PL 00063/0385; Reckitt Benckiser Healthcare (UK) Limited), which was first authorised in the UK on 15 July 2003.

The active ingredient, ibuprofen is a propionic acid derivative, a non-steroidal anti-inflammatory drug (NSAID). It has anti-inflammatory, analgesic and antipyretic properties. It has been investigated in short-term, symptomatic pain relief of mild and moderate pain - such as migraine, dental pain and menstrual pain, and also in the treatment of fever. These effects are seen at daily doses of 1200mg and lower. At higher doses, there is evidence that ibuprofen has an anti-inflammatory action.

No new non-clinical data have been submitted, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years.

A single-dose pivotal bioequivalence study, was submitted to support this application, comparing the pharmacokinetic profile of the test product, Ibuprofen 200mg Tablets (MJK Consultancy Limited), versus the reference products, Nurofen 200mg tablets (Reckitt Benckiser Healthcare B.V., The Netherlands) and Nurofen Express 256mg Capsules (Reckitt Benckiser Healthcare (UK) Limited). The objective of the pharmacokinetic study was to evaluate the bioavailability of the test formulation (2 x 200mg) versus the two reference products, each dosed as 2 x 200mg. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

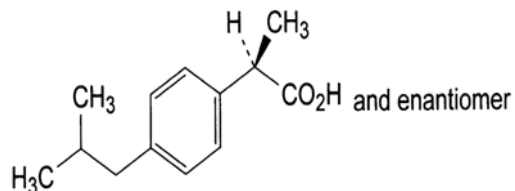
With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Ibuprofen 200mg Tablets outweigh the risks; hence the Marketing Authorisation was granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Ibuprofen
Chemical Name: (2RS)-2-[4-methylpropyl]phenyl]propanoic acid
Structure:



Molecular Formula: $C_{13}H_{18}O_2$
Molecular weight: 206.3
Appearance: A white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in acetone, in methanol and in dichloromethane. 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 European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely sodium hydroxide, glycine, potassium hydroxide, colloidal anhydrous silica, sodium laurilsulphate, mannitol, stearic acid, Macrogol poly (vinyl alcohol) grafted copolymer (Kollicoat IR), basic butylated methacrylate copolymer (Eudragit E PO), ferric oxide red (E172), ferric oxide yellow (E172), titanium dioxide, talc, sucralose, acesulfame potassium, simethicone emulsions and purified water. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Macrogol poly (vinyl alcohol) grafted copolymer (Kollicoat IR), ferric oxide red (E172) and ferric oxide yellow (E172). Macrogol poly (vinyl alcohol) grafted copolymer (Kollicoat IR) complies with its respective Pharmedropa monograph and ferric oxide red (E172), ferric oxide yellow (E172), sucralose and simethicone emulsions are controlled to their respective National Formulary specifications. Ferric oxide red (E172), ferric oxide yellow (E172) are also in compliance with current European Directives concerning use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

No materials of animal or human origin are included in this product.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable product that could be considered comparable in performance to Nurofen Express 256mg Capsules (PL 00063/0374; Reckitt Benckiser (UK) Limited).

Suitable pharmaceutical development data have been provided for this application.

Comparative dissolution profiles have been provided for this product and the respective reference product.

Manufacturing Process

Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation studies were conducted on three pilot-scale batches of each strength and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished Product Specification

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packaged in aluminium/aluminium blister packs. The blister strips are packed in cardboard cartons. Ibuprofen 200mg Tablets (PL 36263/0002) are available in pack sizes of 4, 8, 12, 16 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 foodstuff.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage conditions 'Store in the original package.' has been accepted.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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.

MAA Forms

The MAA form is satisfactory.

Expert Report

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

The grant of Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

As this product is intended for substitution with products that are already marketed, no increase in environmental burden is anticipated and no Environmental Risk Assessment is necessary. A suitable justification has been provided for non-submission of an environmental risk assessment.

CONCLUSION

The grant of Marketing Authorisation is recommended.

CLINICAL ASSESSMENT**CLINICAL PHARMACOLOGY**

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.

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has conducted an open-label, randomised, single-dose, crossover, three-way pivotal bioequivalence study comparing the test product Ibuprofen 200mg Tablets with Nurofen 200mg tablets (Reckitt Benckiser Healthcare B.V, The Netherlands) and Nurofen Express 256mg Capsules (Reckitt Benckiser Healthcare (UK) Limited) in healthy adult subjects under fasted conditions. The objective of the pharmacokinetic study was to evaluate the bioavailability of the test formulation (2 x 200mg) versus the two reference products each dosed as 2 x 200mg.

All volunteers received a single oral dose of either the test or the reference product with 240 ml of water, under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. The washout period of 3 to 7 days was used between each period. A three-way design was used as the study incorporated two reference products.

Results for main pharmacokinetic parameters:

Parent drug

| | Test | Reference 1 (Ibuprofen) | Reference 2 (Sodium ibuprofen) |
|--------------------------|-------------|--------------------------------|---------------------------------------|
| C_{max} (ng/mL) | 43.4 | 31.1 | 38.9 |
| AUC_I (ng.h/mL) | 130.6 | 128.9 | 125.7 |
| AUC_{∞} (ng.h/mL) | 135.6 | 134.1 | 121.9 |
| T_{max} (h)* | 0.54 | 1.61 | 0.83 |

The results for the reference ibuprofen acid product are as expected, as are the AUC results for all products. However, it is noted that the C_{max} is much higher for the test product than for either the ibuprofen acid or the more quickly absorbed sodium ibuprofen. The T_{max} data was expected to differ as the test product has been designed to be absorbed more rapidly than ibuprofen acid.

Bioequivalence results for log-transformed test/reference ratios with 90% confidence intervals are shown below:

Test versus. Reference formulation 1 (Nurofen 200 mg Tablets; ibuprofen)

| Variable | Point estimate (%) | 90 % Confidence limits (%) | Intra-individual CV (%) |
|------------------|---------------------------|-----------------------------------|--------------------------------|
| AUC_{0-last} | 101.28 | 96.77 - 105.99 | 7.2 |
| $AUC_{0-\infty}$ | 101.15 | 96.38 - 106.17 | 7.7 |
| C_{max} | 139.52 | 125.84 - 154.68 | 16.4 |
| $AUC_{0-trun,B}$ | 207.43 | 173.97 - 247.32 | 27.9 |

Test versus. Reference formulation 2 (Nurofen Express 256mg Capsules; sodium ibuprofen)

| Variable | Point estimate (%) | 90 % confidence limits (%) | Intra-individual CV (%) |
|-------------------------|--------------------|----------------------------|-------------------------|
| AUC _{0-last} | 106.76 | 102.07 - 111.67 | 7.2 |
| AUC _{0-∞} | 107.37 | 102.37 - 112.62 | 7.7 |
| C _{max} | 111.08 | 100.34 - 122.98 | 16.4 |
| AUC _{0-trun,B} | 124.73 | 100.89 - 154.19 | 33.9 |

AUC_{0-t} area under the plasma concentration-time curve from time zero to last measurement

AUC_{0-trun,B} area under the plasma concentration-time curve from time zero to truncating B

AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity.

C_{max} maximum plasma concentration

T_{max} time to peak plasma concentration

90% geometric confidence interval (CI) calculated from ln-transformed data

CV Coefficient variant

The 90% confidence intervals for the C_{max} of the test product lie well outside those of the reference product 1. When compared to the faster absorbed reference product 2, the confidence intervals lay within the pre defined acceptance criteria. As expected, bioequivalence was not demonstrated with the reference product 1 (Nurofen 200mg Tablets), due to differing absorption. However, bioequivalence was demonstrated with the second reference product (Nurofen Express 256mg Capsules).

The rate of absorption indicated by maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (t_{max}) were not expected to be equivalent to standard Nurofen (Nurofen 200mg Tablets) as the test product was expected to demonstrate more rapid absorption. Furthermore, Nurofen Express 256mg Capsules were included as a second reference product to show bioavailability of the test product, in the context of another fast acting formulation of ibuprofen, already marketed in the European Union.

EFFICACY

The efficacy of ibuprofen is well-known. No new efficacy data have been submitted and none are required for application of this type.

SAFETY

The Marketing Authorisation Holder has provided relevant data, generated during the bioequivalence study to show that the difference in rate of absorption between the test and reference product will not adversely affect product safety.

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for application of this type. No new or unexpected safety issues were raised by the bioequivalence data.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

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.

CONCLUSION

The grant of Marketing Authorisation is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**QUALITY**

The important quality characteristics of Ibuprofen 200mg Tablets 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. As the pharmacokinetics, pharmacodynamics and toxicology of ibuprofen are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for application of this type.

The bioequivalence study has confirmed that the applicant's 200mg tablet are not bioequivalent to the reference product 1 (Nurofen 200mg Tablets), due to differing absorption. However, bioequivalence was demonstrated with the second reference product (Nurofen Express 256mg Capsules).

SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for application of this type. No new or unexpected safety concerns arose from the bioequivalence study

PRODUCT LITERATURE

The SmPC, PIL and labelling are acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product can be considered equivalent to the reference product, Nurofen 200mg tablets (Reckitt Benckiser Healthcare B.V, The Netherlands). Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.

IBUPROFEN 200MG TABLETS PL 36263/0002

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation application on 12 March 2010.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 26 March 2010.
- 3 Following assessment of the application the MHRA requested further information relating on the quality dossier on 08 April 2010, 16 June 2010 and 14 March 2011, and the clinical dossier on 07 May 2010.
- 4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 14 April 2010, 28 October 2010 and 23 May 2011, and the clinical dossier on 28 October 2010.
- 5 The application was determined and granted on 28 September 2011.

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Ibuprofen 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orange to red oblong, biconvex film-coated tablet with a smooth surface.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Rheumatic and muscular pain, backache, neuralgia, migraine, headache, dental pain, period pain, feverishness, symptoms of colds and influenza.

4.2 Posology and method of administration

For oral administration and short-term use only

Adults, the elderly and children over 12 years:

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Adults and children over 12 years: Initial dose, 200mg to 400mg, (1 or 2 tablets), up to three times a day as required.

Leave at least four hours between doses and do not take more than 1200mg in any 24 hour period. Not for use by children under 12 years of age.

Elderly: No special dosage modifications are required (see Section 4.4).

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to aspirin or other non steroidal anti-inflammatory drugs.

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Patients with severe heart failure, renal failure or hepatic failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

Respiratory:

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Other NSAIDs:

The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:

Systemic lupus erythematosus and mixed connective tissue disease –increased risk of aseptic meningitis (see section 4.8)

Renal:

Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).

Hepatic:

Hepatic dysfunction (see sections 4.3 and 4.8)

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg daily) is associated with an increased risk of myocardial infarction.

Impaired female fertility:

There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Gastrointestinal:

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Dermatological:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. The tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Each tablet contains 23mg (approximately 1mmol) sodium. This should be considered in patients whose overall intake of sodium must be markedly restricted.

The label will include:

Read the enclosed leaflet before taking this product

Do not take if you:

- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen, to any of the ingredients, or to aspirin or other painkillers

- are taking other NSAID pain killers or aspirin with a daily dose above 75mg

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

If symptoms persist or worsen, or if new symptoms occur, consult your doctor or pharmacist.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should not be used in combination with:

- Aspirin unless low-dose aspirin (not above 75mg daily) has been advised by a doctor as this may increase the risk of adverse reactions (see Section 4.4).
- Other NSAIDs, including cyclooxygenase-2 selective inhibitors. Avoid concomitant use of two or more NSAIDs as this may (see Section 4.4)

Ibuprofen should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).
- Antihypertensives and diuretics: NSAIDs may diminish the effects of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4)
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs). Increased risk of gastrointestinal bleeding (see section 4.4).
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- Lithium: There is evidence for potential increases in plasma levels of lithium.
- Methotrexate: There is potential for an increase in plasma methotrexate.
- Ciclosporin: Increased risk of nephrotoxicity
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

4.6 Pregnancy and lactation

No specific studies have been conducted with sodium ibuprofen.

Whilst no teratogenic effects have been demonstrated with ibuprofen acid in animal experiments, the use of the product during pregnancy should, if possible, be avoided during the first 6 months of pregnancy. It should not be used for the last trimester of pregnancy as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child. (see section 4.3).

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at recommended dose and duration of therapy.

4.8 Undesirable effects

Hypersensitivity reactions have been reported and these may consist of

- a) non-specific allergic reactions and anaphylaxis
- b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea

- c) various skin reactions e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Hypersensitivity reactions:

Uncommon: Hypersensitivity reactions with urticaria and pruritis

Very rare: severe hypersensitivity reactions. Symptoms could be facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.

Uncommon: abdominal pain, nausea, dyspepsia

Rare: Diarrhoea, flatulence, constipation and vomiting

Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly (see section 4.4). Ulcerative stomatitis and gastritis.

Exacerbation of colitis and Crohn's disease (section 4.4).

Nervous System:

Uncommon: Headache

Very rare: Aseptic meningitis – single cases have been reported

Renal:

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum and oedema.

Hepatic:

Very rare: liver disorders

Haematological:

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, and agranulocytosis). First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Dermatological:

Uncommon: Various skin rashes.

Very rare: severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Immune System:

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

Cardiovascular and Cerebrovascular:

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke), (see section 4.4).

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms – Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the

prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management – Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivative

ATC code: MO1A E01

Ibuprofen is a non-steroidal anti-inflammatory propionic acid derivative drug (NSAID) that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

5.2 Pharmacokinetic properties

Ibuprofen is absorbed rapidly and entirely from the gastrointestinal tract, is extensively bound to plasma proteins and diffuses into the synovial fluid.

When compared with standard ibuprofen film-coated tablets ibuprofen is significantly faster absorbed from the gastrointestinal tract following the administration of Ibuprofen 200mg tablets (Test formulation), with peak plasma concentrations occurring approximately 30 minutes after administration in the fasting state.

Ibuprofen 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.

Elimination half-life is approximately 2 hours.

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

5.3 Preclinical safety data

No relevant information, additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Glycine,
Potassium hydroxide
Silica, colloidal anhydrous
Sodium Laurilsulphate
Mannitol
Stearic acid
Macrogol poly (vinyl alcohol) grafted copolymer (Kollicoat IR)
Basic butylated methacrylate copolymer (Eudragit E PO)
Ferric Oxide red (E172)
Ferric Oxide Yellow (E172)
Titanium dioxide
Talc
Sucralose
Acesulfame Potassium
Simethicone emulsions
Purified water

- 6.2 Incompatibilities**
Not applicable.
- 6.3 Shelf life**
3 years.
- 6.4 Special precautions for storage**
Store in the original package.
- 6.5 Nature and contents of container**
Alu-Alu blister
The blister trays are packed into either a cardboard carton
Each carton may contain 4, 8, 12, 16 tablets.
- 6.6 Special precautions for disposal**
Not applicable.
- 7 MARKETING AUTHORISATION HOLDER**
MJK Consultancy Ltd
Bickington
Barnstaple
Devon EX31 2JZ
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 36263/0002
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
28/09/2011
- 10 DATE OF REVISION OF THE TEXT**
28/09/2011
- 11 DOSIMETRY (IF APPLICABLE)**
- 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

MODULE 3

The following text is the approved Patient Information Leaflet (PIL) text. No PIL mock-up has been approved. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-up has been obtained

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ibuprofen 200 mg Tablets

Ibuprofen

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take Ibuprofen 200 mg Tablets carefully to get the best results from it.

-
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 10 days.
- **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

In this leaflet:

1. **What Ibuprofen 200 mg Tablets are and what they are used for**
2. **Before you take Ibuprofen 200 mg Tablets**
3. **How to take Ibuprofen 200 mg Tablets**
4. **Possible side effects**
5. **How to store Ibuprofen 200 mg Tablets**
6. **Further information**

1. WHAT IBUPROFEN 200MG TABLETS ARE AND WHAT THEY ARE USED FOR

Ibuprofen 200 mg Tablets contain 200 mg of ibuprofen. Ibuprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). These medicines provide relief by changing the way the body responds to pain and high temperature.

Ibuprofen 200 mg Tablets are used to relieve pain e.g. headache, migraine, dental pain, menstrual pain, rheumatic and muscular pain and to reduce fever.

2. BEFORE YOU TAKE IBUPROFEN 200MG TABLETS

Do not take if you:

- are allergic to ibuprofen or any of the other ingredients in these tablets which are listed in section 6 of this leaflet. An allergic reaction may include worsening of asthma, skin rash, itchy runny nose or swelling of the face, lips
- are allergic to aspirin or other painkillers
- have or have ever had a stomach ulcer, perforation or bleeding
- have had a worsening of asthma, skin rash, itchy runny nose or any facial swelling when you have previously taken ibuprofen, aspirin or other similar kinds of medicines.
- are taking other NSAID painkillers or taking more than 75mg of aspirin
- have severe heart problems, kidney or liver problems.
- are in the last 3 months of pregnancy.
-

Talk with your pharmacist or doctor before taking this product if you:

- are suffering from asthma or have had asthma
- have kidney, liver, heart, or any bowel problems
- have a high cholesterol or you have a high blood pressure
- have diabetes
- have ever had a stroke
- have a history of gastrointestinal disease (such as ulcerative colitis, Crohn's disease)

- if you have Systemic Lupus Erythematosus (a condition which affects the immune system causing joint pain, changes to the skin and other organs)
- if you are a smoker
- if you are in the first 6 months of pregnancy
- if you are on a low sodium diet

Ibuprofen 200mg Tablets belong to a group of medicines which may impair fertility in woman. This is reversible on stopping the medicine. It is unlikely that Ibuprofen 200mg Tablets, used occasionally, will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Do not use the medicine if you are taking other NSAID painkillers or aspirin with a daily dose above 75mg

Ibuprofen 200mg Tablets can stop some other medicines from working properly, especially the following:

- Some anticoagulant medicines (used to thin the blood or prevent clotting) such as aspirin, warfarin, ticlopine
- Some drugs that help reduce high blood pressure (ACE-inhibitors such as catopril, beta-blockers such as atenolol, or angiotensin-II receptor antagonists such as losartan) and other medicines, as these may be affected or may affect by ibuprofen
- corticosteroids, anti-platelet agents, cardiac glycosides, selective serotonin reuptake inhibitors, lithium, methotrexate, Ciclosporin, mifepristone, tacrolimus, Zidovudine or quinolone antibiotics.
- •
- • Taking a painkiller for headaches for too long, can make them worse.
-

Important information about some of the ingredients

This medicine contains 1 mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE IBUPROFEN 200MG TABLETS

This product is for **short-term use** only. You should take the lowest dose for the shortest time necessary to relieve your symptoms.

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

1 or 2 tablets in water, up to three times a day as required

Leave at least 4 hours between doses

Do not take more than 6 tablets in any 24 hours.

Do not give to children under 12 years.

Do not take for longer than 10 days unless your doctor tells you to.

If symptoms persist or the pain or fever worsens, or if any new symptoms occur, consult your doctor or pharmacist.

If you take more Ibuprofen 200mg Tablets than you should

If you take too many tablets, contact your doctor or hospital immediately. Bring any remaining tablets with you

4. POSSIBLE SIDE EFFECTS

Like all medicines, your medicine can cause side effects, although not everybody gets them.

The following side effects are rare (less than 1 in 10,000 people) but if you experience any of the effects the **STOP taking the medicine immediately** and contact your doctor or pharmacist.

- Peptic ulceration or perforation. The symptoms may include severe abdominal pain, vomiting blood (or passing what look like coffee grounds), blood in the faeces (stool/motions) or passing black tarry stools.
- Inflammation of the brain lining. The symptoms may include a stiff neck, headache, nausea, vomiting, fever or feeling disorientated
- Severe allergic reactions. Symptoms include dizziness, fainting, faster heart rate, swelling of the face, throat or tongue.
- Worsening of asthma, wheezing or difficulty in breathing.

Other Possible Side Effects

Less than 1 in 100 people may experience the following uncommon side effects:

- Allergic reactions: Hives, skin rashes and itching
- Stomach: Abdominal pain, indigestion, heartburn and nausea
- Nervous system: Headache

Less than 1 in 1000 people may experience the following rare side effects:

- Diarrhoea, wind, constipation and vomiting.

Less than 1 in 10,000 people may experience the following very rare side effects:

- A reduction in red blood cells which can make the skin pale or yellow, cause fever, sore throat, mild mouth ulcers, flu-like symptoms, exhaustion and weakness, easy bruising
- High blood pressure, heart failure, chest pain
- Nervousness, visual disturbances, ringing in the ears and vertigo
- Liver problems
- Kidney problems.
- Severe skin reactions: symptoms include skin blistering

Medicines such as Ibuprofen may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

If any of the side effects gets serious, or if you notice any side effects on listed on this leaflet, tell your doctor or pharmacist.

5. HOW TO STORE IBUPROFEN 200MG TABLETS

Keep all medicines out of the reach and sight of children.

Do not use Ibuprofen 200mg Tablets after the expiry date which is stated on the carton and blister after {Exp.}. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What your medicine contains

- The active substance is ibuprofen Your medicine contains 200mg Ibuprofen per tablet
- The other ingredients are:
Sodium hydroxide, silicium dioxide, potassium hydroxide, glycine, sodium dodecyl sulphate, mannitol, stearic acid, Kollicoat IR (containing macrogol poly(vinyl alcohol)grafted copolymer), Eudragit E PO (containing basic butylated methacrylate copolymer), iron oxide red, iron oxide yellow, titanium dioxide, talc, sucralose, acesulfam K, simethicone emulsions, water.

What Ibuprofen 200mg Tablets looks like and contents of the pack

The tablets are orange in colour and are available in pack sizes of

Marketing Authorisation Holder and Manufacturer

Your medicine is manufactured by Losan Pharma GmbH, 79395 Neuenburg, Germany

The Marketing Authorisation holder is MJK Consultancy Ltd, Barnstaple, Devon, EX31 2JZ, England

MODULE 4**LABELLING**

The following text is the approved label text. No label mock-ups have been approved. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**BLISTER****1. NAME OF THE MEDICINAL PRODUCT**

[Invented name] 200 mg film-coated tablets

[Invented name] 400 mg film-coated tablets

Ibuprofen

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

N/A

