Public Assessment Report

Decentralised Procedure

Ibuprofen Perrigo 200mg Film-coated Tablets
(ibuprofen lysine)

UK/H/4555/001/DC
UK licence number: PL 12063/0115

Wrafton Laboratories Ltd (t/a Perrigo)
LAY SUMMARY

On 04 April 2012, the MHRA granted Wrafton Laboratories Ltd (trading as Perrigo) a Marketing Authorisation (licence) for the medicinal product, Ibuprofen Perrigo 200mg Film-coated Tablets. This is a medicine available on the General Sales List (GSL), and can be purchased at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist. The product will be referred to as Ibuprofen 200mg Film-coated Tablets in the body of this report.

The active ingredient, ibuprofen, belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), which work to reduce pain and fever.

Ibuprofen 200mg Film-coated Tablets are used for the symptomatic treatment of:
- mild to moderate pain, such as headache, period pain and dental pain.
- fever and pain associated with common cold.

Based on the data submitted by Perrigo, Ibuprofen 200mg Film-coated Tablets were considered to be a generic version of the UK reference product, Nurofen Express 342mg Caplets (PL 00327/0125, Crookes Healthcare Limited).

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Ibuprofen 200mg Film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

## Information about Initial Procedure

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<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<tr>
<td>Active Substance</td>
<td>Ibuprofen (as ibuprofen lysine)</td>
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<td>Form</td>
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<td>Strength</td>
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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Ibuprofen Perrigo 200mg Film-coated Tablets (PL 12063/0115) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Ibuprofen Perrigo 200mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
200mg Ibuprofen (as Ibuprofen Lysine 342mg)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White film coated capsule shaped tablet, embossed on one side with “IBL”.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the symptomatic treatment of mild to moderate pain, such as headache, period pain, dental pain, and fever and pain in the common cold.

4.2 Posology and method of administration
For oral administration and short-term use only.
Adults and adolescents ≥ 40 kg (12 years of age and above):
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.
If this product is required for more than 3 days in the case of fever or for more than 4 days for the treatment of pain, or if the symptoms worsen the patient is advised to consult a doctor.
Take 1 or 2 tablets with water, up to three times a day as required.
Leave at least 6 hours between doses.
Do not take more than 6 tablets in any 24 hour period.
It is recommended that patients with sensitive stomachs take Ibuprofen Perrigo with food.

Special patient groups

Paediatric population:
Not recommended for adolescents weighing under 40 kg or children under 12 years of age.

Elderly Population:
No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal impairment:
No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic impairment (see section 5.2):
No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).
4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angioedema, or urticaria) associated with the intake of acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

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.

Severe hepatic failure, severe renal failure or severe heart failure (see Section 4.4 Special warnings and precautions for use).

Patients with cerebrovascular or other active bleeding.

Patients with blood coagulation disorders.

Patients with unclarified blood-formation disturbances.

Patients with severe dehydration (caused by vomiting, diarrhea or insufficient fluid intake).

Last trimester of pregnancy (see Section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

Caution is required in patients with certain conditions, which may be made worse:

- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).
- Directly after major surgery.
- In patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Ibuprofen Perrigo.
- In patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke’s oedema or urticaria.

Undesirable effects may be minimised by using the lowest effective dose for the shortest 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.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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

SLE and mixed connective tissue disease:
Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

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

Renal:
Hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur.
Renal impairment as renal function may further deteriorate (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

_Hepatic:_

Hepatic dysfunction (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

_Impaired female fertility:_

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

_Gastrointestinal safety:_

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)

Gastrointestinal bleeding, ulceration and perforation: 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 serious gastrointestinal 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.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (See below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 acetylsalicylic acid (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving Ibuprofen Perrigo, the treatment should be withdrawn.

_Skin reactions:_

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 NSAIDSs (see section 4.8). Patients appear to be at highest risk for 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. Ibuprofen Perrigo should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen Perrigo in case of varicella.

_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 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). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg daily) is associated with an increased risk of myocardial infarction.
Other notes:
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering Ibuprofen Perrigo therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

In prolonged administration of Ibuprofen Perrigo regular checking of the liver values, the kidney function, as well as of the blood count, is required.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

Acetylsalicylic acid (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).

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDS including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect (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).

Phenytoin:
The concomitant use of ibuprofen with phenytoin may increase serum levels of both substances. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days).

Antihypertensives and diuretics:
NSAIDs may diminish the effect of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Potassium sparing diuretics:
The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding (See section 4.4 Special warnings).

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4)
Digoxin:
The concomitant use of Ibuprofen Perrigo with digoxin preparations may increase serum levels of these medicinal products. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days).

Lithium:
The concomitant use of Ibuprofen Perrigo with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium is not as a rule required on correct use (maximum over 4 days).

Probenecid and sulfinpyrazone:
Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Methotrexate:
The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

Ciclosporin: Increased risk of nephrotoxicity.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine:
There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Sulphonylureas:
Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.

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 Fertility, Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose
  • the foetus to:
    o cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
    o renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Lactation

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date, so for the short-term treatment with the recommended dose for pain and fever interruption of breast-feeding would generally not be necessary.

4.7 Effects on ability to drive and use machines

As central nervous undesirable effects such as tiredness and dizziness may occur on use of Ibuprofen Perrigo at high dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

For the frequency of occurrence of side effects, the following phrases are used:
  - Very common (≥ 1/10)
  - Common (≥ 1/100 to <1/10)
  - Uncommon (≥ 1/1,000 to <1/100)
  - Rare (≥ 1/10,000 to <1/1,000)
  - Very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most commonly observed adverse reactions are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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 dose (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) (see section 4.4).

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum of 1200 mg ibuprofen for oral dosage forms and a maximum of 1800 mg for suppositories.

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary interindividually.

Infections and infestations:
Very rare: Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal antiinflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal antiinflammatory drugs.

If signs of an infection occur or get worse during use of Ibuprofen Perrigo, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an antiinfective/antibiotic therapy.
The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.

**Blood and Lymphatic System Disorders:**
Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising. In such cases the patient should be advised to discontinue the medicine immediately, to avoid any self-medication with analgesics or antipyretics and to consult a physician. The blood count should be checked regularly in long-term therapy.

**Immune System Disorders:**
Uncommon: Hypersensitivity reactions with skin rashes and pruritus, as well as asthma attacks (possibly with drop in blood pressure), aggravated asthma, bronchospasm, dyspnoea. The patient is to be instructed to inform a doctor at once and no longer to take Ibuprofen Perrigo in this case.

Very rare: Severe general hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

**Psychiatric disorders:**
Very rare: Psychotic reactions, depression.

**Nervous System Disorders:**
Uncommon: Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness.

**Eye disorders:**

**Ear and labyrinth disorders:**
Rare: Tinnitus.

**Cardiac Disorders:**
Very rare: Palpitations, cardiac failure, myocardial infarction.

**Vascular Disorders:**
Very rare: Arterial hypertension.

**Respiratory, Thoracic and Mediastinal Disorders:**
Very rare: Exacerbation of asthma, bronchospasm, dyspnoea.

**Gastrointestinal Disorders:**
Common: Gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.

Uncommon: Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis.

Very rare: Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures. The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.

**Hepatobiliary Disorders:**
Very rare: Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis.

**Skin and Subcutaneous Tissue Disorders:**
Uncommon: Various skin rashes
Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur. Alopecia. In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").

Renal and Urinary Disorders:
Rare: Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely.

Very rare: Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency. Renal function should therefore be checked regularly.

4.9 Overdose
In adolescents and adults the dose response effect is not clear cut in overdose. 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 dizziness, 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: M01AE01

Ibuprofen lysine is the lysine salt of ibuprofen. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans ibuprofen reduces inflammatory-related pain, swellings and fever.

Furthermore, Ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.
5.2 Pharmacokinetic properties

Most pharmacokinetic data obtained following the administration of ibuprofen acid also apply to ibuprofen lysine.

On oral application, ibuprofen is partly absorbed in the stomach and then completely in the small intestine.

Following hepatic metabolism (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90%), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 - 3.5 hours, plasma-protein binding about 99%.

Peak plasma levels following oral administration of a normal-release pharmaceutical form (tablet) when taken with food are reached after 1 - 2 hours.

Peak plasma levels following oral administration of a normal-release pharmaceutical form (tablet) when taken under fasting conditions are reached after 60 to 90 minutes. However ibuprofen is absorbed more rapidly from the gastrointestinal tract following oral administration of Ibuprofen Perrigo with peak plasma levels following oral administration under fasting conditions reached after 30 minutes (median). Ibuprofen is detected in the plasma for more than 8 hours after administration of Ibuprofen Perrigo.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments showed up mainly in form of lesions and ulcerations in the gastrointestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to an inhibition of ovulation in rabbits as well as disturbances of implantation in various animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits have demonstrated that ibuprofen crosses the placenta. For maternally toxic doses, an increased incidence of malformations (ventricular septal defects) was observed in the progeny of rats.

The active substance ibuprofen shows an environmental risk to fish.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Crospovidone
Copovidone
Microcrystalline Cellulose
Magnesium Stearate

Coat
Opadry II White*

* Contains the constituents; polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
A blister pack consisting of white opaque PVC/PVdC blister with aluminium foil. The blisters are packed in cardboard cartons.

Pack sizes: 8, 12 or 16 tablets

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Wrafton Laboratories Ltd (Trading as Perrigo)
Wrafton
Braunton
Devon
EX33 2DL, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 12063/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/04/2012

10 DATE OF REVISION OF THE TEXT
04/04/2012
Module 3

Patient Information Leaflet – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

Ibuprofen Perrigo 200mg Film Coated Tablets
For adults and adolescents weighing from 40 kg body weight (12 years of age and above)

Ibuprofen Lysine

Patient Information Leaflet

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
- You must talk to a doctor if your symptoms worsen or do not improve after 3 days when you are suffering from a fever or 4 days when you are suffering from pain.

In this leaflet:

1. What this medicine is for
2. Before you take the medicine
3. How to take the medicine
4. Possible side effects
5. Storing the medicine
6. Further information

1. WHAT THIS MEDICINE IS FOR

This medicine contains ibuprofen lysine which is the lysine salt of ibuprofen. Ibuprofen is one of a group of non-steroidal anti-inflammatory drugs (known as NSAIDS) which work to reduce pain and fever.

This medicine is used for the symptomatic treatment of:

- mild to moderate pain, such as headache, period pain and dental pain
- fever and pain associated with common cold.

2. BEFORE YOU TAKE THE MEDICINE

Do not take this medicine if you:

- are allergic to ibuprofen or any of the other ingredients of this medicine (listed in section 6)
- have ever suffered from shortness of breath, asthma, a runny nose, swelling or hives after using acetylsalicylic acid (known as aspirin) or other similar painkillers (NSAIDs)
- have (or have had two or more episodes of) a stomach ulcer, or bleeding of the stomach
• have a history of gastro-intestinal bleeding or perforation related to previous NSAID therapy
• have severe kidney or severe heart failure or severe liver failure
• are bleeding, including any bleeding within the brain (cerebrovascular bleeding)
• are suffering from blood clotting disorders
• suffer from a currently undiagnosed problem with your body’s ability to form blood
• are severely dehydrated (caused by vomiting, diarrhoea or insufficient fluid intake)
• are in the last 3 months of pregnancy

Talk to your doctor or pharmacist before taking ibuprofen tablets if you:
• if you suffer from serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. The use of Ibuprofen Tablets should be stopped immediately at the first appearance of skin rash, mucosal lesions, or any other signs of allergic reactions
• if you have hereditary blood formation disorder (acute intermittent porphyria)
• if you are elderly because you may be at more risk of having side effects, particularly stomach problems
• if you have or have suffered from asthma or have allergies as shortness of breath may occur
• if you suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders an increased risk of allergic reactions exists. The allergic reactions may present as asthma attacks (so-called analgesic asthma). Quincke’s oedema or urticaria
• during chickenpox (varicella) it is advisable to avoid use of Ibuprofen Tablets
• if you have reduced liver or kidney function
• directly after major surgery
• if you have stomach or bowel disorders including Crohn’s disease or a condition known as ulcerative colitis
• if you have Systemic Lupus Erythematosus (SLE) or mixed connective tissue disease – an illnesses which affects your immune system. They It causes joint pains, skin changes and problems with other parts of your body.
• if you have, have previously had, or are at risk of heart problems, high blood pressure or stroke. Medicines such as Ibuprofen Tablets may be associated with a small increased risk of heart attack (“myocardial infarction”) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment (3 days in the treatment of fever and 4 days in the treatment of pain). If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist
• In prolonged administration of Ibuprofen Tablets regular checking of your liver values, the kidney function, as well as of the blood count, is required
• The use with concomitant NSAIDs, including cyclo-oxygenase-2 specific inhibitors, increases risk of adverse reactions (see section “If you are taking other medicines” below) and should be avoided.
Undesirable effects are minimised by using the minimum effective dose for the shortest period of time.

In general the habitual use of (several sorts of) analgesics can lead to lasting severe kidney problems. This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Consult a doctor before using Ibuprofen Tablets if any above mentioned conditions concerns you.

If you are taking other medicines
What should you avoid when you are taking other medicines?
Some medicines that are anti-coagulants (against clotting) (e.g. acetylsalicylic acid, warfarin, ticlopidin), some medicines against high blood pressure (ACE-inhibitors e.g. captopril, beta-receptor blocking medicines, angiotensin II antagonists), and even some other medicines may effect or be effected by the treatment of ibuprofen. Seek therefore always advice of a doctor before you use ibuprofen with 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. In particular, tell them if you are taking:

- acetylsalicylic acid, or other NSAIDs (anti-inflammatories and analgesics) since this may increase the risk of gastrointestinal ulcers or bleeding
- digoxin (for heart insufficiency) since the effect of digoxin may be enhanced
- glucocorticoids (medicinal products containing cortisone or cortisone-like substances) since this may increase the risk of gastrointestinal ulcers or bleeding
- anti-platelet agents since this may increase the risk of bleeding
- acetylsalicylic acid (low dose) since the blood-thinning effect may be impaired
- medicines for thinning the blood (such as warfarin) since ibuprofen may enhance the effects of these medicines
- phenytoin (for epilepsy) since the effect of phenytoin may be
selective serotonin reuptake inhibitors (medicines used for depression)

as these may increase the risk of gastrointestinal bleeding

lithium (a medicine for manic depressive illness and depression)
since the effect of lithium may be enhanced

probenecid and sulfipyrazone (medicines for gout)
since the excretion of ibuprofen may be delayed

medicines for high blood pressure and water tablets
since ibuprofen may diminish the effects of these medicines and there could be a possible increased risk for the kidney

potassium sparing diuretics
since this may lead to hyperkalaemia

methotrexate (a medicine for cancer or rheumatism)
since the effect of methotrexate may be enhanced

tacrolimus and cyclosporine (immunosuppressive medicines)
since kidney damage may occur

zidovudine: (a medicine for treating AIDS)
since the use of Ibuprofen Tablets may result in an increased risk of bleeding into a joint or a bleeding that leads to swelling in HIV (+) haemophiliacs

sulfonylureas (antidiabetic medicines)
interactions may be possible

quinolone antibiotics
since the risk for convulsions may be increased

**Taking Ibuprofen Tablets with food and drink**
It is recommended that patients with sensitive stomachs take Ibuprofen Tablets with food. Some side effects, such as those affecting the gastrointestinal system can be more likely when alcohol is taken at the same time as Ibuprofen Tablets.

**Pregnancy and Breast feeding**
Tell your doctor if you become pregnant during intake of this medicine. Do not take this medicine if you are in the last 3 months of pregnancy. Talk to your doctor before taking ibuprofen tablets if you are in the first 6 months of pregnancy.

This medicine may be used during breast feeding for a maximum of 3 days (when you are treating a fever) or 4 days (for the treatment of pain), as only small amounts of this medicine passes into breast milk.
These tablets belong to a group of medicines, which may impair fertility in women. This is reversible on stopping the medicine. It is unlikely that the tablets, used occasionally, will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

3. HOW TO TAKE THE MEDICINE

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with doctor or pharmacist if you are not sure.

<table>
<thead>
<tr>
<th>Body weight (Age)</th>
<th>Dose and how often to take</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, and adolescents weighing from 40 kg (12 years old and above)</td>
<td>Take 1 or 2 tablets with water, every 6 hours, as required. Do not take more often than every 6 hours. Do not take more than 6 tablets in any 24 hour period.</td>
</tr>
</tbody>
</table>

The tablets are intended for short-term use only. Use them for the shortest time needed to relieve symptoms. Always use the lowest dose that relieves your symptoms. Talk to your doctor if symptoms worsen or you need to take these tablets for more than 3 days when you have a fever or 4 days when you are suffering from pain.

**Do not give to adolescents weighing under 40 kg or children under 12 years.**

For oral use.

Please speak to the doctor or pharmacist if you feel that the effect of this medicine is greater or less than you expected.

**If you take too many tablets:** Talk to a doctor straight away, or go to your nearest hospital casualty department. Take the carton and this leaflet with you. The following signs may occur: nausea, vomiting, stomach pain, diarrhoea, ringing in the ear, headache, gastrointestinal bleeding, dizziness, drowsiness, confusion, disorientation. Rarely: loss of consciousness.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ibuprofen Tablets can cause side effects, although not everybody gets them.

Side effects may be minimised by taking the lowest dose for the shortest time necessary to relieve the symptoms. You may suffer one of the known side effects of NSAIDs (see below). If you do, or if you have concerns, stop taking this medicine and talk to your doctor as soon as possible. Elderly people using this product are at increased risk of developing problems associated with side effects.
The following frequencies are taken as a basis when evaluating side effects:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>common</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>uncommon</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>rare</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>very rare</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>not know</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

STOP TAKING this medicine and seek immediate medical help if you develop:

- **signs of intestinal bleeding** such as severe pain in the abdomen, black tarry stools, vomiting blood or dark particles that look like coffee grounds.
- **signs of very rare but serious allergic reaction** such as worsening of asthma or shorness of breath, swelling of the face, tongue or throat, difficulty breathing, racing heart, drop in blood pressure leading to shock. These can happen even on first use of this medicine.
- severe skin reactions such as rashes covering the whole body, peeling, blistering or flaking skin.

Tell your doctor if you have any of the following side effects, they become worse or you notice any effects not listed.

**Common**

- gastrointestinal complaints, such as heart burn, abdominal pain, feeling sick and indigestion, vomiting, wind (flatulence), diarrhoea, constipation, and slight blood losses in stomach and/or bowel that may cause anaemia in exceptional cases.

**Uncommon**

- stomach or intestinal ulcers, sometimes with bleeding and perforation, inflammation of the lining of the mouth with ulceration (ulcerative stomatitis), inflammation of the stomach (gastritis), worsening of colitis and Crohn's disease
- central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
- visual disturbances
- allergic reactions, such as skin rashes, itching and asthma attacks. You must stop taking Ibuprofen Tablets and inform your doctor at once.

**Rare**

- tinnitus (ringing in the ears)
- kidney damage (papillary necrosis) and elevated uric acid concentrations in the blood

**Very rare**

- swelling (oedema), high blood pressure (hypertension) and cardiac failure have been reported in association with NSAID treatment.
• inflammation of the oesophagus or pancreas, formation of membrane-like narrowing in the small and large intestines (intestinal, diaphragm-like strictures)
• serious infections of the skin and soft-tissue complications have occurred during chicken pox (varicella) infection.
• passing less urine than normal and swelling (especially in patients with high blood pressure or reduced kidney function): swelling (oedema) and cloudy urine (nephrotic syndrome); inflammatory kidney disease (interstitial nephritis) that may lead to acute kidney failure. If one of the above mentioned symptoms occur or if you have a general miserable feeling, stop taking Ibuprofen Tablets and consult your doctor immediately as these could be first signs of a kidney damage or kidney failure.
• problems in the blood cell production - first signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding. In these cases you must stop the therapy immediately and consult a doctor. Any self-treatment with pain killers or medicinal products that reduce fever (antipyretic medicinal products) mustn’t be done.
• psychotic reactions and depression
• exacerbation of infection-related inflammations (e.g. necrotising fasciitis) associated with use of certain painkillers (NSAIDs) has been described. If signs of an infection occur or get worse during use of Ibuprofen Tablets, you must go to a doctor without delay. It is to be investigated whether there is an indication for an antiinfective/antibiotic therapy.
• high blood pressure, palpitations, heart failure, heart attack.
• liver dysfunction, liver damage, especially during long-term treatment, liver failure, acute inflammation of the liver (hepatitis)
• the symptoms of aseptic meningitis with neck stiffness, headache, feeling sick, being sick, fever or consciousness clouding have been observed when using ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) may be more likely to be affected. Contact a doctor at once, if these occur.
• severe forms of skin reactions such as skin rash with redness and blistering (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis/Lyell’s syndrome), hair loss (alopecia).
• severe general hypersensitivity reactions.
• worsening of asthma, bronchospasm, dyspnoea.

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

5. STORING THE MEDICINE

Do not use after the expiry date shown on the pack.
Store in the original container.
Keep all medicines out of the reach and sight of children.

6. FURTHER INFORMATION
What is in this medicine:
The active ingredient is: Ibuprofen 200 mg (as ibuprofen lysine 342 mg) per coated tablet.
The other tablet core ingredients are: Crospovidone, copovidone, microcrystalline cellulose and magnesium stearate.
The tablet coating ingredient is: Opadry II White (contains polyvinyl alcohol, titanium dioxide E171, macrogol 3350 and talc).

What this medicine looks like and contents of the pack:
Each tablet is a film-coated white tablet, embossed with 'IBL' on one side.
This product is available in a pack size of 8, 12 or 16 tablets. Not all pack sizes may be marketed.
Marketing Authorisation Holder and Manufacturer: Wrafton Laboratories Limited (Trading as Perrigo), Braunton, Devon, EX33 2DL, United Kingdom.

Date of revision: 03/2012

PL 12063/0115
Module 4

Labelling – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Perrigo 200mg film coated Tablets
Ibuprofen Lysine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: 200 mg Ibuprofen (as Ibuprofen lysine 342 mg).

3. LIST OF EXCIPIENTS

N/a

4. PHARMACEUTICAL FORM AND CONTENTS

8 film coated tablets
12 film coated tablets
16 film coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow the tablets whole with water. Do not chew. Read the package leaflet before use. Refer to your doctor or pharmacist if in doubt.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/a

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
N/a

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

N/a

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Ltd (Trading as Perrigo)
Wrafton
Braunton
Devon
EX33 2DL, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 12063/0115

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

This medicine is used to relieve the symptoms of mild to moderate pain, such as headache, period pain and toothache and reduce the fever and pain associated with the common cold.

**DOSAGE**

**Adults, and adolescents weighing from 40 kg (12 years old and above):** Take 1 or 2 tablets with water every 6 hours, as required. Leave at least 6 hours between doses. Do not exceed 8 tablets in 24 hours.

**Do not give to adolescents weighing under 40 kg or children under 12 years.**

**WARNINGS**

Do not exceed the stated dose. Take the lowest effective dose needed to relieve your symptoms, as this product is intended for short-term use only. Talk to your doctor or pharmacist if your symptoms worsen or you need to take these tablets for more than 3 days when you have a fever or 4 days when you are suffering from pain.

16. INFORMATION IN BRAILLE

Ibuprofen Perrigo 200mg film coated Tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

### 1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Perrigo 200mg film coated Tablets
Ibuprofen Lysine

### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Wraffton Laboratories Ltd (Trading as Perrigo)

### 3. EXPIRY DATE

EXP:

### 4. BATCH NUMBER

BN:

### 5. OTHER

N/A
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Wrafton Laboratories Ltd (trading as Perrigo) a Marketing Authorisation (MA) for the medicinal product, Ibuprofen Perrigo 200mg Film-coated Tablets (PL 12063/0115; UK/H/4555/001/DC), on 04 April 2012. The product is available on a General Sales Licence (GSL).

This is a generic application for Ibuprofen Perrigo 200mg Film-coated Tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK product, Nurofen Express 342mg Caplets (PL 00327/0125), authorised to Crookes Healthcare Limited on 27 July 2000. The UK reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired. The originator product is Dolormin Schmerztabletten 200mg filmtabletten (200mg, film coated tablet), authorised to McNeil GmbH since 28/09/1995.

With the UK as the Reference Member State (RMS) in this Decentralised procedure, Wrafton Laboratories Ltd applied for a Marketing Authorisation for Ibuprofen Perrigo 200mg Film-coated Tablets in Czech Republic, Germany, Hungary, Italy, Netherlands and Poland.

Ibuprofen Perrigo 200mg Film-coated Tablets are indicated for the symptomatic treatment of mild to moderate pain, such as headache, period pain, dental pain, and fever and pain associated with the common cold.

Ibuprofen lysine is the lysine salt of ibuprofen. Ibuprofen (ATC classification: M01AE01) is a non-steroidal anti-inflammatory drug (NSAID) that, in the conventional animal-experiment inflammation models, has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Ibuprofen 200mg Film-coated Tablets, to that of the reference product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Ibuprofen Perrigo 200mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Ibuprofen (as ibuprofen lysine) |
| Pharmacotherapeutic classification (ATC code) | Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives (M01AE01) |
| Pharmaceutical form and strength(s) | Film-coated Tablets 200 mg ibuprofen (as 342 mg ibuprofen lysine) |
| Reference numbers for the Mutual Recognition Procedure | UK/H/4555/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | CZ, DE, HU, IT, NL, PL |
| Marketing Authorisation Number(s) | PL 12063/0115 |
| Name and address of the authorisation holder | Wrafton Laboratories Ltd (Trading as Perrigo) Wrafton Braunton Devon EX33 2DL, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Ibuprofen lysine

Nomenclature:

INN: Ibuprofen lysine
Chemical names: lysine salt of 2(4-isobutylphenyl) propionic acid
Molecular formula: C₁₉H₃₂N₂O₄
Molecular weight: 352.48 g/mol
CAS No: 57469-76-8
Physical form: A white powder
Solubility: Soluble in water (1% w/v) and in methanol (1% w/v)

Ibuprofen lysine is not the subject of a British Pharmacopoeia (BP) or European Pharmacopoeia (Ph. Eur) monograph. Ibuprofen, however, is the subject of a Ph. Eur monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer(s) during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.
MEDICINAL PRODUCT

Description and Composition

Ibuprofen 200mg Film-coated Tablets are presented as white, film-coated, capsule shaped tablets, embossed on one side with “IBL”. Each tablet contains 200 mg of the active ingredient, ibuprofen (as ibuprofen lysine 342 mg).

Other ingredients consist of pharmaceutical excipients, namely crospovidone, copovidone, microcrystalline cellulose and magnesium stearate making up the tablet cores; and polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc constituting the film coating, “Opadry II White”. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs, with the exception of the film-coating, Opadry II White, which is controlled to satisfactory in-house specifications. The constituents of the film-coating comply with their respective Ph. Eur monographs.

Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, generic, immediate-release, tablet formulation of ibuprofen lysine 342 mg, bioequivalent to the UK reference product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited).

Comparative dissolution data were provided for batches of the test product and an appropriate reference product. The dissolution profiles were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished product specification

Finished product specifications are provided for release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Ibuprofen Perrigo 200mg Film-coated Tablets are licensed for marketing in polyvinylidene chloride (PVdC)-polyvinylchloride (PVC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 8, 12 or 16 tablets.
Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 36 months. This medicinal product does not require any special storage conditions.

**Quality Overall Summary**

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The labelling texts fulfil the statutory requirements for Braille.

The PIL text is in line with the SmPC and is satisfactory. User-testing of the PIL text has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Ibuprofen 200 mg tablets (PL 16028/0013). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated product. The bridging is accepted.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Ibuprofen 200mg Film-coated Tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of ibuprofen, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited).

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of Ibuprofen 200mg Film-coated Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INTRODUCTION

Ibuprofen lysine is a salt of ibuprofen (a propionic acid derivative) which demonstrates faster systemic absorption from the gut. It is used as an analgesic, anti-inflammatory and antipyretic. It is available widely as both a prescription medicine and over the counter, with both P and GSL licenses granted in the UK.

INDICATIONS

Ibuprofen 200mg Film-coated Tablets are indicated for the symptomatic treatment of mild to moderate pain, such as headache, period pain, dental pain, and fever and pain associated with the common cold.

The indications are satisfactory. They match those of the originator product, are consistent with those of the UK reference product and are also in line with MHRA guidelines on minimal clinical particulars for ibuprofen P and GSL licences.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the originator product and is satisfactory.

CLINICAL PHARMACOLOGY

The clinical pharmacology of ibuprofen is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.

Clinical pharmacodynamics

Ibuprofen has analgesic, antipyretic and anti-inflammatory activities. It is a potent inhibitor of cyclo-oxygenase (COX), thus causing a marked decrease in prostaglandin synthesis. This decreases the hyperalgesic effect of prostaglandins as well as their vasodilator effect, thereby decreasing the sensation of pain and inflammation. It also inhibits synthesis of some lipoxygenases and has been shown at high concentrations to reduce toxin release from leucocytes and inhibit the migration of polymorphs.
**Interactions:** Aspirin displaces ibuprofen from its plasma binding sites and produces a significant reduction in plasma ibuprofen levels. Ibuprofen, at high doses (over 2684 mg daily) has an adverse effect on the plasma levels of methotrexate, lithium and digoxin. It leads to a need to close monitoring in the first two. Rhabdomyolysis and renal failure have been linked to an interaction between ibuprofen and ciprofibrate. Ibuprofen may interact with drugs used in the treatment of hypertension and oedema, leading to fluid retention and renal insufficiency.

**Clinical pharmacokinetics**

**Absorption** - ibuprofen is rapidly absorbed after ingestion. The lysine salt has faster absorption (C_{max} 15-40 minutes after dosing) than the standard ibuprofen acid tablets (C_{max} 60-120 minutes after dosing). Absorption is delayed (lower C_{max} and later T_{max}) but not reduced when taken after food. Absorption is known to be non-linear with regards to dose levels.

**Distribution** - ibuprofen has a low volume of distribution (~0.1 l.kg^{-1}) and has high plasma protein binding levels. There is minimal passage into breast milk but it is well distributed into cerebrospinal and synovial fluid.

**Metabolism** - ibuprofen undergoes extensive metabolism in the liver, mainly by cytochrome P450 2C9. The main metabolites are 2-[4-(hydroxyl-2-methylpropyl)phenyl]-propionic acid and 2-[4-(carboxypropyl)phenyl]propiolic acid, both of which are conjugated with glucuronic acid before excretion. None of the metabolites are active.

**Excretion** - less than 10% of the original dose is excreted unchanged by the kidneys. Elimination from plasma is rapid, at around 2 hours. The metabolites are mainly excreted in the urine (90%), with the rest in the faeces.

**Pharmacokinetics – bioequivalence study**

The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Ibuprofen 200mg Film-coated Tablets, to that of the reference product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, laboratory-blinded, two-treatment, two-sequence, two-period, single dose crossover bioequivalence study conducted in healthy adult human subjects under fasting conditions. Following an overnight fast, a single 200 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 12.0 hours after administration of test or reference product. Plasma levels of ibuprofen were detected by a validated HPLC method.

The primary pharmacokinetic parameters for the study were C_{max}, AUC_{0-t}, and AUC_{0-\infty}. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed C_{max}, AUC_{0-t}, and AUC_{0-\infty} for ibuprofen.
Results:
An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for ibuprofen for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=12 hours; washout period: 7 days

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reference product (X)</td>
<td>Test product (Y)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>24.34</td>
<td>25.83</td>
</tr>
<tr>
<td>AUC0-t (ng.h/ml)</td>
<td>65.65</td>
<td>64.67</td>
</tr>
<tr>
<td>AUC0-∞ (ng.h/ml)</td>
<td>68.01</td>
<td>67.15</td>
</tr>
</tbody>
</table>

Discussion on Bioequivalence
The results of the bioequivalence study show that Ibuprofen 200mg Film-coated Tablets and Nurofen Express 342mg Caplets (Crookes Healthcare Limited) are bioequivalent, under fasting conditions, as the confidence intervals for Cmax, AUC0-t, and AUC0-∞ fall within the acceptance criteria ranges of 80-125% in line with current guidelines.

CLINICAL EFFICACY
No new data have been submitted and none are required. The reference product is established and the application is supported by the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of ibuprofen is well-established from its extensive use in clinical practice.

Ibuprofen has been available on the market for a number of decades now and its efficacy in a number of indications is well understood. In a clinical study of professional football players with lower limb injuries it was found that ibuprofen was more effective than aspirin, significantly reducing the duration and severity of pain as well as allowing them to return back to activity earlier. In a study in patients with non-articular rheumatism (e.g. bursitis, fibrositis, myalgia and tenosinovitis), it was shown that ibuprofen was as effective as indomethacin. A long term study of 585 patients with osteoarthritis of the knee indicated that oral and topical ibuprofen were both effective, although oral treatment was associated with a greater number of adverse events. In patients with rheumatoid arthritis ibuprofen (at 1200-1600 mg daily) was found to be as effective and well-tolerated as fenoprofen, naproxen and tolmetin. In a review of 34 studies, involving 3591 patients, ibuprofen 684 mg was found to be superior to placebo and as good as diclofenac 50 mg as analgesia following dental surgery. A meta-analysis of 6 studies comparing ibuprofen to paracetamol indicated a similar efficacy with regards to antipyretic effects at 1 hour. Ibuprofen was found to have a greater mean temperature reduction at 4-6 hours after administration.
CLINICAL SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of ibuprofen is well-known.

The safety profile of ibuprofen and its salts is well known. They have been available for a number of decades now, as over the counter medicines as well as by prescription. The most well known and serious reaction is that of gastrointestinal haemorrhage. A study demonstrated that ibuprofen showed a 1.5% incidence of GI haemorrhage (haematemesis or melena), peptic ulceration, gastric pain or vomiting, compared to 1% for placebo and 12.5% for aspirin. Hepatic and renal events, although rare, have been recorded. Renal failure has been reported, especially in those with underlying renal disease. This is thought to be due to the fact that the renal blood flow in these patients is only maintained because of prostaglandin release, which is inhibited by ibuprofen. Hypersensitivity reactions can occur and bronchospasm can be seen in patients with asthma. Urticaria, angioedema, purpura, photosensitivity and bullous dermatitis have also been recorded in the literature. Haematological abnormalities have also been seen, including thrombocytopenia, aplasia and haemolysis. Low dose ibuprofen is felt to be safe in pregnancy, although its use is not recommended. Its use in the last 3 months of pregnancy is contra-indicated as it can cause premature closure of the foetal ductus arteriosus and also delay the onset of labour, increase its duration and cause an increased bleeding tendency in both mother and child. In overdose, the toxic effects of ibuprofen are generally mild and only require supportive treatment. In more severe cases hypotension, acidosis, renal and hepatic dysfunction and GI haemorrhage are seen. Large overdoses identified early can be treated with lavage.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet
The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling
The labelling text is satisfactory.

CONCLUSIONS

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ibuprofen 200mg Film-coated 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 and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Ibuprofen Perrigo 200mg Film-coated Tablets, and the reference product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The PIL text is in line with the SmPC and is satisfactory. User-testing of the PIL text has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Ibuprofen 200 mg tablets (PL 16028/0013). The results show that the leaflet 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.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Ibuprofen 200mg Film-coated Tablets is a generic version of the reference product, Nurofen Express 342mg Caplets (Crookes Healthcare Limited). Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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