Public Assessment Report

Decentralised Procedure

Ibuprofen 200 mg/5 ml Oral Suspension

UK/H/3267/002/DC

UK licence number: PL 04917/0100

Pinewood Laboratories Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Pinewood Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Ibuprofen 200 mg/5 ml Oral Suspension (PL 04917/0100) on 29th September 2011. This is a prescription-only medicine (POM).

The active ingredient, ibuprofen, belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen 200mg/5ml Oral Suspension is given to children under 12 as a painkiller for relief of mild to moderate muscular pain, headache, teething pain and toothache. It also reduces the temperature in fever (e.g. colds, influenza and post-immunisation fever). For adults and children over 12 it can be used for backache, migraines, neuralgia and relief from non-serious arthritic conditions.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Ibuprofen 200 mg/5 ml Oral Suspension outweigh the risk, hence a Marketing Authorisation has been granted.
## Module 1
### Information about Initial Procedure

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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Ibuprofen 200 mg/5 ml Oral Suspension (PL 04917/0100) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
   Ibuprofen 200 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each 5ml contains 200mg of Ibuprofen.
   Excipients:
   Liquid Maltitol  4.25g/5ml
   For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
   Oral Suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
   Children under 12 years
   Rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia), symptoms of cold and influenza.
   Over 12 years
   Rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

4.2 Posology and method of administration
   For oral administration and short-term use only.
   Leave at least four hours between doses and do not take more than the recommended amount in any 24 hour period.
   Not to be given to children under 3 months of age, except on the advice of a doctor
   This product should only be given to infants who weigh more than 5kg.
   If the child’s (aged over 6 months) symptoms persist for more than 3 days, consult your doctor promptly. For children aged 3 to 6 months, medical advice should be sought promptly after 24 hours symptoms persist.
   The daily dosage for children is 20- 30mg/kg bodyweight in divided doses. Using the dosing device provided this can be achieved as follows:
   3 to 6 months (weighing more than 5 kg): 1.25ml (50mg), up to 3 times in 24 hours.
   6 to 12 months (weighing 8-10 kg): 1.25ml (50mg), up to 3 to 4 times in 24 hours.
   1 to 4 years (weighing 10-15 kg): 2.5ml (100mg), up to 3 times in 24 hours.
   4 to 7 years (weighing 15-20 kg): 3.75ml (150mg), up to 3 times in 24 hours.
   7 to 12 years (weighing 20-40 kg): 5 ml (200mg), up to 3 times in 24 hours.
   Over 12 years: 5 ml (200mg) to 10ml (400mg) up to three times in 24 hours (maximum daily dose 1200mg)
   Post-immunisation pyrexia in infants
   1.25ml as a single dose repeated once after 6 hours if necessary.
   No more than 2 doses in 24 hours. If fever is not reduced, consult a doctor.
   This product is intended for short term use only. Only the lowest dose for the shortest time necessary to relieve symptoms should be used.
Children over 6 months to 12 years should not take Ibuprofen 200mg/5ml Oral Suspension for longer than 3 days unless your doctor tells you to.

Those aged 12 years or over should not take Ibuprofen 200mg/5ml Oral Suspension for longer 10 days unless your doctor tells you to.

Impaired renal function
In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. (For patients with severe renal failure see section 4.3)

Impaired liver function
In patients with mild or moderate reduction of liver function the dose should be kept as low as possible for the shortest duration necessary to control symptoms and hepatic function monitored. (For patients with severe liver failure see section 4.3)

If symptoms persist or worsen consult your doctor.

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

Patients with a history of bronchospasm asthma, rhinitis, or urticaria associated with the intake of aspirin (acetylsalicylic acid) or other non-steroidal anti-inflammatory drugs (NSAIDs).

History of gastrointestinal bleeding or perforation, related to NSAID’s therapy.

Last trimester of pregnancy (see section 4.6).

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

Severe hepatic failure, severe renal failure or severe heart failure or coronary heart disease (see section 4.4).

Suspected haemopoietic disorder.

Cerebrovascular or other active bleeding.

Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use
Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2 GI and cardiovascular risks below)

Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events

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

Other NSAIDs:
The use of Ibuprofen 200 mg/5 ml Oral Suspension with concomitant NSAIDs including cylooxygenase-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).

Asthmatic patients are to seek their doctor’s advice before using ibuprofen (see below)
Renal:
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8)
Administration of NSAIDs such as Ibuprofen may cause dose dependent renal toxicity in patients with reduced renal blood flow or blood volume where renal prostaglandins support the maintenance of renal perfusion. Patients at risk of this reaction include those with impaired renal function, heart failure or liver dysfunction. This is of particular importance in hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur. Caution is therefore required in the use of Ibuprofen in such patients.

Hepatic:
Hepatic dysfunction (see section 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 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.

Respiratory:
Ibuprofen should be used with caution in patients with bronchial asthma or allergic disease, since such patients may have NSAID – sensitive asthma which has been associated with severe bronchospasm.

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 serious GI events.

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

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 medicinal products likely to increase gastrointestinal risk (see below and section 4.5).

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.

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 NSAIDs (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 200mg/5ml Oral Suspension should be discontinued at the first appearance of skin rash, mucosal lesion, 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 Oral Suspension in case of varicella (Chicken pox.)
During the prolonged use of analgesics headaches may occur which must not be treated with elevated doses of the medicinal product. In general the habitual intake of analgesics, particularly the combination use of different analgesic substances, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration therefore it should be avoided.

Ibuprofen may temporarily inhibit the blood platelet function (thrombocyte aggregation) and prolong the bleeding time. Patients with coagulation defects or on anticoagulant therapy should be observed carefully.

In case of prolonged treatment with ibuprofen a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients.

Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially if affecting the gastrointestinal tract or the central nervous system.

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking/administering Ibuprofen, therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Caution is required in the following patients:
- patients with congenital disorder of porphyrim metabolism (e.g. acute intermittent porphyria)
- patients who are dehydrated
- patients directly after major surgical procedures

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Aspirin: Unless low-dose aspirin (not above 75 mg 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: as a results of synergistic effects, avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4). Co-administration of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4)

Ticlopidine: NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Methotrexate: There is a potential for an increase in plasma methotrexate.

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4). In case of simultaneous treatments, monitoring of the coagulation state is recommended.

Diuretics, ACE inhibitors, beta-receptor blocking medicines and angiotensin-II antagonists:
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. 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, beta-receptor blocking medicines 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.
The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia.

**Sulphonylureas:**
Clinical investigations have shown interactions between NSAIDs 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.

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

**Corticosteroids:** May increase the risk of adverse reactions in the gastrointestinal tract (see section 4.4 Special warnings).

**Anti-platelets 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 increased plasma glycoside levels.

**Ciclosporin:** Increased risk of nephrotoxicity.

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

**Lithium, Phenytoin:** There is evidence for potential increase in plasma levels of these active ingredients. Checking the serum lithium levels is necessary and it is recommended to check the serum phenytoin levels.

**Methotrexate:** There is potential of an increase in plasma methotrexate.

**Zidovudine:** Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of 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 quinolone may have increased risk of developing convulsions.

**Ritonavir:** May increase the plasma concentrations of NSAIDs.

**Moclobemide:** Enhances the effect of ibuprofen.

**Captopril:** Experimental studies indicate that ibuprofen counteracts the effect of captopril on increased sodium excretion.

**Aminoglycosides:** NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.

**Cholestyramine:** Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least one hour interval.

**Alcohol, bisphosphonates and oxpentifylline (pentoxyflline):** May potentiate the GI side-effects and the risk of bleeding and ulceration.

**Baclofen:** Elevated baclofen toxicity.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development.
Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis 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-fetal 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 trimesters 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 trimesters 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 fetus to:
- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- 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:*
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect breast-fed infants adversely. If, however, longer treatment is prescribed, early weaning should be considered.

*Fertility:*
The use of ibuprofen may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

### 4.7 Effects on ability to drive and use machines

None expected at recommended dose and duration of therapy

### 4.8 Undesirable effects

The following frequencies are taken as a basis when evaluating undesirable effects:

**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

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

The most commonly observed adverse events 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, melaena, 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.

Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.

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).
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

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 (= 60 ml oral suspension of Ibuprofen Oral Suspension maximum daily dose for adults and children older than 12 years).

**Infections and infestations:**
Very rare: exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of this product, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.

Very rare: the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousnesses 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, and 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 rash and pruritis, as well as asthma attacks (possibly with drop in blood pressure). The patient is to be instructed to inform a doctor at once and no longer to take Ibuprofen in this case.

Very rare: Severe general hypersensitivity reactions. They may present as facial oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening 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:**
Uncommon: visual disturbances.

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

**Cardiac disorders**
Very rare: palpitations, heart failure, myocardial infarction.

**Vascular disorders**
Very rare: arterial hypertension.
Gastrointestinal disorders:
Common: gastrointestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, 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, photosentivity
Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis 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: renal tissue damage (papillary necrosis), particularly in long-term therapy, increased serum uric acid concentration in the blood.

Very rare: reduced urinary excretion and 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.

Investigations
Rare: increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, prolonged bleeding time, decrease of serum calcium, increase in serum uric acid

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 derivatives

ATC Code: M01 AE01

Ibuprofen 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.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose if ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreases effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitation 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 effects is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Absorption

On oral application ibuprofen is already partly absorbed in the stomach and then completely in the small intestine, peak serum concentrations occurring 1-2 hours after oral administration of a normal-release pharmaceutical form.

Distribution

Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%.

Metabolism

Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination

Ibuprofen is metabolised in the live into two major metabolites with primary excretion via the kidneys. Either as such or as major conjugates, together with negligible amount of unchanged Ibuprofen, Excretion by the kidney is both rapid and complete. Elimination half life is approximately 2 hours.

5.3 Preclinical safety data

As a well established and widely used product, the pre-clinical safety of ibuprofen is well documented.

The principal findings observed during subchronic and chronic toxicity studies with ibuprofen include gastric damage and ulcers. Any observation made during the in vitro and in vivo studies to investigate the mutagenic potential of ibuprofen were not considered to be clinically significant.

Furthermore no carcinogenic effects have been observed in mice and rats. Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reprotoxicity studies in rats and rabbits; ibuprofen crossed the placenta. At dose causing toxicity to the mother, malformations (ventricular septal defects) occurred more frequently in the progeny of rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Xanthan gum,
Liquid Maltitol,
Polysorbate 80,
Saccharin sodium,
Citric acid monohydrate (for pH-adjustment),
Magnesium Aluminium Silicate,
Sodium Benzoate (E211),
Strawberry flavour (contains propylene glycol)
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months
In use shelf life: 3 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original pack.

6.5 Nature and contents of container
An amber glass bottle sealed with child resistant, tamper evident cap.
Pack sizes available: 60 ml, 80ml, 100 ml, 150 ml and 200 ml.
Not all pack sizes may be marketed.
A double ended spoon with measures of 1.25ml 2.5ml or 5ml is provided.

6.6 Special precautions for disposal
Shake well before use. Return any left over medicine to the Pharmacist for safe disposal.

7 MARKETING AUTHORITYHOLDER
PINEWOOD LABORATORIES LIMITED
BALLYMACARBRY
CLONMEL
CO TIPPERARY
IRELAND

8 MARKETING AUTHORITY NUMBER(S)
PL 04917/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
29/09/2011

10 DATE OF REVISION OF THE TEXT
29/09/2011
_MODULE 3_

**Product 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.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Ibuprofen 200 mg/5 ml Oral Suspension**

*Read all of this leaflet carefully before you start taking/giving this medicine. 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 symptoms persist or worsen after 1 day (infants aged 3-6 months) or 3 days (children aged 6 months to 12 years) or 10 days (for those aged over 12 years)
- 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 200mg/5ml Oral Suspension is and what it is used for
2. Before you give/take Ibuprofen 200mg/5ml Oral Suspension
3. How to give/take Ibuprofen 200mg/5ml Oral Suspension
4. Possible side effects
5. How to store Ibuprofen 200mg/5ml Oral Suspension
6. Further information

1. **WHAT IBUPROFEN 200MG/5ML ORAL SUSPENSION IS AND WHAT IT IS USED FOR**

Ibuprofen 200 mg/5 ml Oral Suspension contains Ibuprofen as the active ingredient. This belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

Ibuprofen 200mg/5ml Oral Suspension is given to children under 12 as a painkiller for relief of mild to moderate muscular pain, headache, teething pain and toothache. It also reduced the temperature in fever (e.g. colds, influenza and post-immunisation fever). For adults and children over 12 it can also be used for backache, migraines, neuralgia and relief from non-serious arthritic conditions.

2. **BEFORE YOU GIVE/TAKE IBUPROFEN 200MG/5ML ORAL SUSPENSION**

**Do NOT give/take this medicine if you or your child:**
- has an allergy or hypersensitivity to ibuprofen or any of the other ingredients in this medicine (see Section 6 and Section 2: Important information about ingredients)
- has had an allergic reaction or wheezing e.g. an asthma attack runny nose, skin reaction or swelling after taking aspirin or other non-steroidal anti-inflammatory painkillers
- has ever had a stomach ulcer or a history of bleeding into, or perforation of, the intestine especially after previous NSAID treatment
- is taking any other non-steroidal anti-inflammatory pain killers (NSAIDs)
- has ever had severe kidney, heart or liver problems
- is suffering from severe dehydration
- has an inherited intolerance to some sugars
- is less than 3 months old, except on the advice of a doctor
- suffers from a blood disorder
- are in the last three months of pregnancy
- are trying to conceive
Take special care and check with your doctor or pharmacist before taking this medicine if you are elderly or your child suffers from:

- high blood pressure, heart problems or a stroke because there is a small increased risk of heart problems and stroke with ibuprofen
- kidney, liver or bowel problems
- lupus (SLE) or a mixed connective tissue disease
- a chronic inflammatory bowel disease such as ulcerative colitis, Crohn's disease
- asthma or allergic diseases of the lungs
- has a disorder of porphyrin metabolism

Speak to your doctor or pharmacist before taking if you are trying to get pregnant. Ibuprofen belongs to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine, it is unlikely that ibuprofen, used occasionally, will affect your chances of becoming pregnant, however, tell your doctor before taking this medicine if you have problems becoming pregnant.

If any of these apply, ask for advice from a doctor or pharmacist before using this medicine.

Medicines such as Ibuprofen 200mg/5ml Oral Suspension 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. If you have heart problems, previous stroke or if you think you or your child might be at risk of these conditions (for example if you or your child have high blood pressure diabetes, high cholesterol or are a smoker) you should discuss the treatment with your doctor or pharmacist.

Drinking alcohol while taking Ibuprofen may increase your risk of certain side effects.

Taking other medicines
Please tell your doctor or pharmacist if you or your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor if you or your child is taking any of the following:

- Low-dose aspirin (up to 75 mg a day)
- Diuretics (drug to help you pass water)
- Anticoagulants e.g. Warfarin and Heparin and Anti-platelet drugs such as Clopidogrel and Ticlopidine (drugs that thin the blood)
- Antihypertensives (drugs used to treat high blood pressure e.g. Captopril or Propranolol)
- Lithium, Phenytoin or Selective serotonin reuptake inhibitors (SSRI’s e.g. Fluoxetine - used to treat mood disorders)
- Methotrexate (used to treat rheumatoid arthritis, psoriasis and some cancers)
- Zidovudine (used to treat HIV)
- Corticosteroids (anti-inflammatory drugs, such as prednisone)
- Cardiac glycosides (drugs used in the treatment of heart problems, such as Digoxin)
- Ciclosporin or Tacrolimus (used to suppress the body’s immune system)
- Quinolone antibiotics (used to treat a wide range of infections e.g. Ciprofloxacin)
- Probenecid and sulfinpyrazone (used to treat gout)
- Moclobemide (used to treat depression)
- Aminoglycosides (and antibiotic)
• Cholestyramine (used to reduce cholesterol)
• Baclofen (used to relax muscles)
• Sulphonylureas (used to treat diabetes)
• Ritonavir (used to treat HIV infection and AIDS)
• Bisphosphonates (used to prevent loss of bone mass)
• Ospetifylline (used to treat poor circulation to arms and legs)
• Any other Ibuprofen preparations or NSAID painkillers, including those you can buy without a prescription.

If you are not sure about any of the medicines your child is taking, ask your pharmacist for advice.

Pregnancy and breast-feeding
Ibuprofen should NOT be taken during the last 3 months of pregnancy, as it may be harmful to the unborn child. Pregnant women intending to use this product should seek medical advice before use as it should only be taken on doctor’s advice during the first 6 months of pregnancy.

Only small amounts of ibuprofen and its break down products pass into breast milk. As no harmful effects to infants are known to date, it is not usually necessary to stop breast-feeding during short-term use of ibuprofen at the recommended doses.

Important information about some of the ingredients of this medicine
• Maltitol (E965) may have a mild laxative effect (caloric value 2.3 kcal/g). If you have been told that you or your child have an intolerance to some sugars, contact your doctor before taking/giving this medicine.

3. HOW TO GIVE/TAKE IBUPROFEN 200MG/5ML ORAL SUSPENSION

Shake the bottle well before measuring the dose. A measuring device is provided to ensure accuracy.

Contact a doctor for advice if symptoms persist or worsen for more than 10 days in those aged over 12 years. For children aged 6 months to 12 years contact a doctor if symptoms persist or worsen after 3 days. For infants aged 3 months to 6 months contact a doctor if symptoms persist or worsen after 24 hours.

This medicine should NOT be given if your child weighs less than 5 kg. The usual daily dose in children is 20 - 30 mg per kg of bodyweight in divided doses. Leave at least 4 hours between doses. For oral and short term use only.

WARNING: DO NOT EXCEED THE STATED DOSE

<table>
<thead>
<tr>
<th>Babies under 3 months</th>
<th>Do not give except on the advice of a doctor</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - 6 months (weighing more than 5 kg)</td>
<td>1.25 ml dose (50 mg) taken up to 3 times in 24 hours</td>
</tr>
<tr>
<td>Age</td>
<td>Dose Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>1.25 ml dose (50 mg) taken up to 3 times in 24 hours</td>
</tr>
<tr>
<td>(weighing 8-10 kg)</td>
<td></td>
</tr>
<tr>
<td>1 - 4 years</td>
<td>2.5 ml dose (100 mg) taken up to 3 to 4 times in 24 hours</td>
</tr>
<tr>
<td>(weighing 10-15 kg)</td>
<td></td>
</tr>
<tr>
<td>4 - 7 years</td>
<td>3.75 ml dose (150 mg) taken up to 3 times in 24 hours</td>
</tr>
<tr>
<td>(weighing 15-20 kg)</td>
<td></td>
</tr>
<tr>
<td>7 - 12 years</td>
<td>5 ml dose (200 mg) taken up to 3 times in 24 hours</td>
</tr>
<tr>
<td>(weighing 20-40 kg)</td>
<td></td>
</tr>
<tr>
<td>Over 12 years</td>
<td>5 ml to 10 ml dose (200 mg - 400 mg) taken 3 times in 24 hours. Do not give more than 30 ml (1200 mg) in any 24 hours.</td>
</tr>
</tbody>
</table>

**Post-immunisation fever:** One 1.25 ml, followed by another 1.25 ml six hours later if necessary. Not more than 2 doses should be given in 24 hours. If fever is not reduced, consult a doctor.

**If you forget to give/take this medicine**
If you forget to give/take a dose, give/take it as soon as you remember, unless it is almost time for the next dose. Never give a double dose to make up for the missed dose.

**If you give/take more medicine than you should**
If you or your child takes a lot more than the stated dose (an overdose), you should contact a doctor immediately, or go to the nearest hospital casualty department, and take the bottle with you if you can.

4. **POSSIBLE SIDE EFFECTS**
Like all medicines, Ibuprofen can cause side-effects, although not everybody gets them.
The most common side-effect is irritation of the stomach which can cause problems in some patients.

**If any of the following occur, stop giving/taking the medicine and seek immediate medical help:**
- Passing blood in the stools (faeces/motions)
- Passing black tarry stools
- Vomiting blood or dark particles that look like coffee grounds
- Unexplained wheezing, shortness of breath, skin rash (which may be severe and include blister or peeling of the skin), itching or bruising, light-headedness, racing of the heart or fluid retention e.g. swollen ankles, not passing enough water
- Stiff neck, headache, nausea, vomiting, fever and disorientation
- Swelling of the face

**any of the following occur, stop giving/taking the medicine and tell your doctor:**
- If you or your child's skin start to turn red or they develop a varied skin reaction or their skin starts to blister or peel, this is very rare.
- Unexplained stomach pain, indigestion, heartburn, feeling sick and/or vomiting
- Yellowing of the eyes and/or skin
- Severe sore throat with high fever or unexplained bleeding, bruising and tiredness

**Other unusual effects may include the following:**
**Uncommon:**
- Headache, dizziness, sleeplessness, agitation, irritability or tiredness
- Visual disturbances
  
  Rare:
  - Flatulence, diarrhoea or constipation
  - Ringing in ears (tinnitus)
  - Kidney damage, increased blood uric acid levels
  
  Very Rare:
  - Occasionally hypersensitivity reactions may occur which can cause skin rashes as well as asthma attacks, swelling of the tongue and breathlessness
  - Liver problems may occur with ibuprofen
  - Passing less urine than normal, increased proteins in the blood (detected by tests)
  - Crohn's disease or ulcerative colitis or other stomach problems may be exacerbated
  - Ibuprofen 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.
  - Depression or psychotic reactions
  - Hair loss
  - High blood pressure.

If any of these side effects gets worse, or if you notice a side effect not listed in this leaflet, tell your doctor or pharmacist.

5. **HOW TO STORE IBUPROFEN 200MG/5ML ORAL SUSPENSION**

Keep out of the reach and sight of children. Do not use after the expiry date shown on the bottle, the expiry date refers to the last day of that month. Do not store above 25°C. Medicines should not be disposed of via wastewater, ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Ibuprofen 200mg/5ml Oral Suspension contains

The active ingredient is Ibuprofen 200 mg per 5 ml.

The other ingredients are: Glycerol, Xanthan Gum, Maltitol (E965), Polysorbate 80, Saccharin Sodium (E954), Citric Acid Monohydrate, Sodium benzoate (E211), Magnesium Aluminium Silicate, Purified Water and Strawberry Flavour (contains Propylene glycol).

What Ibuprofen 200MG/5ML Oral Suspension looks like and contents of the pack

Ibuprofen 200mg/5ml Oral Suspension is a colour-free, white oral suspension. This medicine comes in amber glass bottles containing: 60 ml, 80ml 100 ml, 150 ml or 200 ml, with a child-resistant closure. Not all pack sizes may be marketed. A double ended spoon with measures of 1.25ml, 2.5ml and 5ml is provided. This medicine should be used within 3 months of first opening.

**Marketing Authorisation Holder**

PINEWOOD LABORATORIES LIMITED
BALLYMACARBRY
CLONMEL
CO TIPPERARY
IRELAND

**Manufacturer**

To be completed nationally

This medical product is authorised in the member states of the EEA under the following names:

FI: Burana 40mg/ml Oralisuspensio
LT: IbuViva Forte 200mg/5ml geriamojo suspensija

**PL Number:**

This leaflet was last approved in 08/2011
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.

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

[Carton]

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 200mg/5ml Oral Suspension

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5 ml of the oral suspension contains 200 mg of the active Ibuprofen

3. LIST OF EXCIPIENTS

Also includes Maltitol (E965 and Sodium benzoate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60ml oral suspension
80ml oral suspension
100 ml oral suspension
150 ml oral suspension
200 ml oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

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

WARNING: DO NOT EXCEED THE STATED DOSE

Read the package leaflet before use

8. EXPIRY DATE

EXP. MM/YYYY
This medicine should be used within 3 months of first opening

9. SPECIAL STORAGE CONDITIONS

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

To be completed nationally
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PINEWOOD LABORATORIES LIMITED
BALLYMACARBY
CLONMEL
CO TIPPERARY
IRELAND

12. MARKETING AUTHORISATION NUMBER(S)

PL 04917/0100

13. BATCH NUMBER

B/N: XXXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally

15. INSTRUCTIONS ON USE

Shake the bottle well before use. Please use measuring device provided

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - 6 months (weighing more than 5 kg)</td>
<td>1.25 ml dose (50 mg) taken up to 3 times in 24 hours</td>
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<td>5 ml to 10ml dose (200mg – 400mg) taken 3 times in 24 hours. Do not give more than 30 ml (1200 mg) in any 24 hours.</td>
</tr>
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</table>

Do not give to babies under 3 months, except on the advice of a doctor.

Post-immunisation fever. 1.25ml followed by another 1.25ml six hours later if necessary. Not more than 2 doses should be given in 24 hours. If fever is not reduced, consult a doctor.

16. INFORMATION IN BRAILLE

Ibuprofen 200mg/5ml Suspension
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

[Label] PL04917/0099, PL04917/0100 and PL04917/0121

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 200mg/5ml Oral Suspension

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5 ml of the oral suspension contains 200 mg of the active Ibuprofen

3. LIST OF EXCIPIENTS

Also includes maltitol (E965) and Sodium Benzoate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60ml oral suspension
80ml oral suspension
100 ml oral suspension
150 ml oral suspension
200 ml oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

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.
This medicine should be used within 3 months of first opening

7. OTHER SPECIAL WARNING(S) IF NECESSARY

WARNING: DO NOT EXCEED THE STATED DOSE

8. EXPIRY DATE

EXP: MM/YYYY
9. SPECIAL STORAGE CONDITIONS

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

To be completed nationally

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PINEWOOD LABORATORIES LIMITED
BALLYMACARBRY
CLONMEL
CO TIPPERARY
IRELAND

12. MARKETING AUTHORISATION NUMBER(S)

PL 04917/0100

13. BATCH NUMBER

B/N: XXXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Pinewood Laboratories Limited a Marketing Authorisation for the medicinal product, Ibuprofen 200 mg/5 ml Oral Suspension (PL 04917/0100, UK/H/3267/002/DC), on 29th September 2011. The product is a prescription-only medicine.

This is an abridged application for Ibuprofen 200 mg/5 ml Oral Suspension, submitted under Article 10.3 of 2001/83 EC, as amended. This hybrid application makes reference to the UK product, Nurofen 200 mg Tablets (PL 00065/0385), licensed to Reckitt Benckiser Healthcare (UK) Ltd. on 29th January 2011. The cross-referenced product was initially authorised to Crookes Healthcare Limited (PL 00327/0146) on 15th July 2003 as a line-extension to the original Marketing Authorisation for Nurofen 200 mg Tablets (PL 00327/0004, Crookes Healthcare Limited), granted on 6th May 1983. PL 00327/0146 underwent a Change of Ownership (CoA) procedure to the current Reckitt Benckiser Healthcare (UK) Ltd licence on 29th January 2011. The originator UK reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised Procedure, Pinewood Laboratories Limited applied for a Marketing Authorisation for Ibuprofen 200 mg/5 ml Oral Suspension in Finland and Lithuania.

Ibuprofen 200 mg/5 ml Oral Suspension is indicated in children under 12 years of age for rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia) and symptoms of cold and influenza. The medicinal product is also indicated in patients over 12 years of age for rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

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, which is acceptable given that this was a hybrid application cross-referring to 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 200 mg/5 ml Oral Suspension, to that of the reference product, Nurofen 200 mg Tablets (Reckitt Benckiser Healthcare (UK) Ltd.). 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. 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 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a medicinal 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.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). 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.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ibuprofen 200 mg/5 ml Oral Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anti-inflammatory and antirheumatic products, non steroids; propionic acid derivatives (M01AE01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Oral suspension 200 mg/5 ml</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3267/002/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>FI and LT</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 04917/0100</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pinewood Laboratories Limited</td>
</tr>
<tr>
<td></td>
<td>Ballymacarbry</td>
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<td></td>
<td>Clonmel</td>
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<td>Co Tipperary</td>
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<tr>
<td></td>
<td>Ireland</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Ibuprofen

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

```
CH3
H3C
CH3

H

CO2H
```

Molecular formula: C₁₃H₁₈O₂
Molecular weight: 206.3 g/mol
CAS No: 15687-27-1
Physical form: A white or almost white, crystalline powder
Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in dichloromethane

The active substance, ibuprofen, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of ibuprofen are supported by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability (CEP). The certificates are accepted as confirmation of the suitability of ibuprofen for inclusion in this medicinal product.

The retest periods proposed are supported by satisfactory information.
MEDICINAL PRODUCT

Description and Composition

Ibuprofen 200 mg/5 ml Oral Suspension is a white or cream-coloured oral suspension with a strawberry flavour, packed into 60mL, 80mL, 100mL, 150mL or 200mL amber glass bottles with polypropylene caps. Each 5 ml of solution contains 200 mg ibuprofen.

Other ingredients consist of pharmaceutical excipients, namely glycerol, xanthan gum, liquid maltitol, polysorbate 80, saccharin sodium, citric acid monohydrate (for pH-adjustment), magnesium aluminium silicate, sodium benzoate (E211), strawberry flavour (contains propylene glycol) and purified water. 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 strawberry flavour, which complies with satisfactory in-house specifications. 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 aim was to produce a stable, acceptably tasting oral suspension, containing 200mg of ibuprofen in every 5mL.

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 on pilot-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished Product Specifications

Finished product specifications are provided for both 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 200 mg/5 ml Oral Suspension is licensed for marketing in 60mL, 80mL, 100mL, 150mL or 200mL amber glass bottles, sealed with child-resistant, tamper-evident, polypropylene caps. The bottles are packaged with the Patient Information Leaflet (PIL) and
a double-ended spoon (with measures of 1.25 ml 2.5 ml or 5 ml) into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed.

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 24 months for the unopened bottle (3 months once the bottle is opened), with the storage instructions ‘Do not store above 25°C. Store in the original pack’.

**Quality Overall Summary**

A satisfactory quality overview 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 labelling text fulfils the statutory requirements for Braille.

The user-testing of the PIL text has been accepted based on a bridging report provided by the applicant making reference to the successful user-testing of the PIL for Ibuprofen 100 mg/5 ml Paediatric Oral Suspension (PL 04917/0080). The text, content and layout of the proposed PIL are considered sufficiently similar to the approved PIL for the reference product. The bridging is accepted.

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.

**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 200 mg/5 ml Oral Suspension 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 a hybrid application, referring to a medicinal 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 overview, dated February 2010, cites 21 references from the published literature dated up to year 2010. The CV of the non-clinical expert has been supplied. For applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the originator product, Nurofen 200 mg Tablets (Reckitt Benckiser Healthcare (UK) Ltd).

There are no objections to approval of Ibuprofen 200 mg/5 ml Oral Suspension from a non-clinical point of view.

III.3 CLINICAL ASPECTS

CLINICAL BACKGROUND

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) that has well established analgesic and antipyretic properties and is widely available worldwide.

INDICATIONS

Ibuprofen 200 mg/5 ml Oral Suspension has the following indications:

Children under 12 years
Rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia), symptoms of cold and influenza.

Over 12 years
Rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

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

TOXICOLOGY

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

CLINICAL PHARMACOLOGY

The clinical pharmacology of ibuprofen is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.
The primary mechanism of action is thought to be via inhibition of cyclo-oxygenase 2 (COX-2) but there is also inhibition of leucocyte accumulation/activation and cytokine production, e.g. interleukin 1β, tumour necrosis factor α, nitric oxide and leukotriene B₄. The pharmacodynamic half-life has been shown to be around 6-8 hours.

Ibuprofen is rapidly absorbed after oral ingestion of solutions, salts of ibuprofen or gelatin capsules (C_max 15-40 minutes post dosing) whereas standard tablet formulations are absorbed somewhat more slowly (C_max 60-120 min). Food is known to delay absorption.

However, the extent of oral absorption seems to be unaffected by the nature of the formulation. Ibuprofen has a relatively low solubility yet high permeability. A single bioequivalence study comparing the proposed formulation against a suitable reference formulation has therefore been conducted.

Ibuprofen undergoes extensive (approx. 90% of the dose) metabolism to inactive substances, mainly glucuronic acid conjugates via hepatic CYP 2C9.

Elimination is rapid with a half-life of approximately 2 hours. Less than 10% is excreted unchanged in the urine.

Pharmacokinetics – bioequivalence study

The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Ibuprofen 200 mg/5 ml Oral Suspension, to that of the clinical reference product, Nurofen 200 mg Tablets (Reckitt Benckiser Healthcare (UK) Ltd.). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was a randomised, open-label, two-treatment, two-sequence, two-period, two-way, single-dose crossover bioequivalence study conducted in healthy, adult human male and female subjects under fasting conditions. Following an overnight fast, a single dose of the investigational products was administered orally, with water, to each subject in each period. A satisfactory washout period of 48 hours was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 12.0 hours after administration of test or reference product. Plasma levels of ibuprofen were quantified by a validated HPLC bioanalytical method.

The primary pharmacokinetic parameters for this study were C_max, AUC₀₋₄, and AUC₀₋∞. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_max, AUC₀₋₄, and AUC₀₋∞.

Results:

Safety –There were no deaths or serious or significant adverse events. The test and reference products were comparable in their safety and tolerability.

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. Wash-out period: 48 hours.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
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<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>18.28</td>
<td>17.31</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/ml)</td>
<td>59.20</td>
<td>55.66</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/ml)</td>
<td>61.29</td>
<td>57.90</td>
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$C_{\text{max}}$ maximum plasma concentration
$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the 90% confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ for ibuprofen fall within the acceptance criteria ranges of 80-125% in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98).

Clinical efficacy

No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of ibuprofen is well-established from its extensive use in clinical practice.

Clinical safety

No new safety 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.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Product Information Leaflet (PIL)

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

Labelling

The labelling text is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview, dated February 2010, cites 221 references from the published literature dated up to year 2010. The CV of the clinical expert has been supplied.
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 200 mg/5 ml Oral Suspension 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 200 mg/5 ml Oral Suspension and the reference product, Nurofen 200 mg Tablets (Reckitt Benckiser Healthcare (UK) Ltd.).

No new or unexpected safety concerns arise from this application.

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

The final 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 PIL for Ibuprofen 100 mg/5 ml Paediatric Oral Suspension (PL 04917/0080). The bridging is accepted.

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 qualitative and quantitative assessment supports the claim that the applicant’s Ibuprofen 200 mg/5 ml Oral Suspension is therapeutically equivalent to the reference product, Nurofen 200 mg Tablets (Reckitt Benckiser Healthcare (UK) Ltd.). 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

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<th>Date submitted</th>
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<th>Scope</th>
<th>Outcome</th>
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