Public Assessment Report

Decentralised Procedure

Nurofen Express Soluble 400mg Oral Powder
Nurofen Express 400mg Oral Powder

UK/H/3534 & 3996/001/DC

UK licence no: PL 00063/0611 & 0616

Reckitt Benckiser Healthcare (UK) Limited
LAY SUMMARY

On 28\textsuperscript{th} November 2011, the UK granted Reckitt Benckiser Healthcare (UK) Limited Marketing Authorisations (licences) for Nurofen Express Soluble 400mg Oral Powder/Nurofen Express 400mg Oral Powder.

Nurofen Express Soluble 400mg Oral Powder/Nurofen Express 400mg Oral Powder contain the active ingredient ibuprofen. Ibuprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

These medicines provide relief by changing the body’s response to pain, swelling and high temperature.
Nurofen Express is used to relieve:
• Symptoms of mild to moderate pain such as headache, toothache, period pains, rheumatic and muscular pain and migraine.
• Cold and flu symptoms such as sore throat and fever.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Nurofen Express 400mg Oral Powder/Nurofen Express Soluble 400mg Oral Powder outweigh the risks; hence these Marketing Authorisations have been granted.
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  3 Non-clinical aspects
  4 Clinical aspects
  5 List of outstanding issues
Module 6 Steps taken after initial procedure ......................................... Not applicable
Module 1

Information about the initial procedure

| **Product Name** | Nurofen Express Soluble 400mg Oral Powder  
Nurofen Express 400mg Oral Powder |
<table>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Known active substance, Article 8.3</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Ibuprofen Lysinate</td>
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<tr>
<td><strong>Form</strong></td>
<td>Oral Powder</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>400mg</td>
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</tbody>
</table>
| **MA Holder** | Reckitt Benckiser Healthcare (UK) Ltd  
Dansom Lane  
Hull  
HU8 7DS |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/3534/001/DC: The Czech Republic (CZ), Hungary (HU), Ireland (IE), the Netherlands (NL), Poland (PL), Romania (RO) and the Slovak Republic (SK)  
UK/H/3996/001/DC: Poland (PL) |
| **Procedure Number** | UK/H/3534/001/DC  
UK/H/3996/001/DC |
| **End of Procedure** | Day 210: 21st September 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Nurofen Express Soluble 400mg Oral Powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains Ibuprofen 400mg (as Ibuprofen lysinate).

Excipient(s):
Sucrose 1.26g/sachet
Tartrazine 0.0067 mg/sachet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral powder
A white, lemon flavoured powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of mild to moderate pain associated with headache, migraine, backache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms such as sore throat and fever.

4.2 Posology and method of administration
For oral administration and short-term use only.
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 5 days when treating pain and 3 days when treating fever.

Adults, the elderly and children aged over 12 years
Initial dose - one sachet. Then, if necessary, one sachet up to three times a day as required.
Dissolve the contents of the sachet in a glass of water, stir, and then drink immediately.
Leave at least six hours between doses. Do not exceed more than 3 sachets (1200mg) in any 24 hour period.

Special patient groups:
Elderly:
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 insufficiency:
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 insufficiency (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).

Children and adolescents:
Not to be given to children under 12 years of age.

4.3 Contraindications
Patients with a known hypersensitivity to ibuprofen, tartrazine (E102) or any of the constituents in the product.
Patients with a history of bronchospasm, asthma, rhinitis, angioedema or urticaria associated with acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs).
History of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
Patients with severe hepatic failure, severe renal failure or severe heart failure.
In patients with cerebrovascular or other active bleeding.
In patients with coagulation disorders or bleeding diathesis.
In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).
During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

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

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See Section 4.2).

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

Other NSAID’s:
Use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

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

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

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

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

Impaired female fertility:
There is 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 the treatment.

Gastrointestinal:
NSAID’s 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 (GI) bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time 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 and 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 4.5).

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.

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 (SSRIs) or anti-platelet agents such as aspirin (See Section 4.5).

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

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Nurofen Express Soluble 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 Nurofen Express Soluble in case of varicella.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

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<thead>
<tr>
<th>Concomitant use of ibuprofen with</th>
<th>Possible effects:</th>
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<tr>
<td>Other NSAIDs, including salicylates:</td>
<td>The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).</td>
</tr>
<tr>
<td>Digoxin:</td>
<td>The concomitant use of Nurofen Express Soluble 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).</td>
</tr>
<tr>
<td>Corticosteroids:</td>
<td>Corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal; ulceration or bleeding) (see section 4.3)</td>
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<tr>
<td>Anti-platelet agents:</td>
<td>Increased risk of gastrointestinal bleeding (see section 4.4).</td>
</tr>
<tr>
<td>Acetylsalicylic acid (low dose):</td>
<td>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).</td>
</tr>
<tr>
<td>Anticoagulants:</td>
<td>NSAIDs may enhance the effect of anti-coagulants, such as warfarin and heparin (see section 4.4). Monitoring of</td>
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coagulation state is recommended in case of simultaneous treatment.

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<tr>
<th>Medication/Interaction</th>
<th>Description</th>
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<tr>
<td><strong>Phenytoin:</strong></td>
<td>The concomitant use of Nurofen Express Soluble with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not as a rule required on correct use.</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs):</strong></td>
<td>Increased risk of gastrointestinal bleeding (see section 4.4).</td>
</tr>
<tr>
<td><strong>Lithium:</strong></td>
<td>The concomitant use of Nurofen Express Soluble 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).</td>
</tr>
<tr>
<td><strong>Probenecid and sulfinpyrazone:</strong></td>
<td>Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.</td>
</tr>
<tr>
<td><strong>Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists:</strong></td>
<td>NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. 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 cyclooxygenase 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.</td>
</tr>
<tr>
<td><strong>Potassium sparing diuretics:</strong></td>
<td>The concomitant administration of Nurofen Express Soluble and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).</td>
</tr>
<tr>
<td><strong>Methotrexate:</strong></td>
<td>The administration of Nurofen Express Soluble within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.</td>
</tr>
<tr>
<td><strong>Ciclosporin:</strong></td>
<td>The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.</td>
</tr>
<tr>
<td><strong>Tacrolimus:</strong></td>
<td>The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.</td>
</tr>
<tr>
<td><strong>Zidovudine:</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Sulphonylureas:</strong></td>
<td>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</td>
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of blood-glucose values is recommended as a precaution on concomitant intake.

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<tr>
<th>Quinolone antibiotics:</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mifepristone</strong></td>
<td>NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.</td>
</tr>
</tbody>
</table>

4.6 **Fertility, pregnancy and lactation**

**Fertility**

See section 4.4 regarding female fertility.

**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, Nurofen Express should not be given unless clearly necessary. If Nurofen Express 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: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamnionis;

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, Nurofen Express Soluble 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 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 Nurofen Express Soluble 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**

Hypersensitivity reactions have been reported and these may consist of:
Non-specific allergic reactions and anaphylaxis
Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
Various skin reactions e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The following list of adverse effects relates to those experienced with ibuprofen at 400mg per single dose up to 1200mg maximum daily dose, for short term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Please note that within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| Infections and infestations | Very rare | Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs. If signs of an infection occur or get worse during use of Nurofen Express Soluble 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. 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, nose and skin bleeding. |
| Immune system disorders | Uncommon | Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure) |
| Psychiatric disorders | Very rare | Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). |
| | Very rare | Psychotic reactions, depression |
### Nervous System disorders
- **Uncommon**: Headache, dizziness, sleeplessness, tinnitus, tiredness, agitation, irritability
- **Very rare**: Aseptic meningitis – single cases have been reported very rarely.

### Eye disorder
- **Uncommon**: Visual disturbances

### Ear and labyrinth disorders
- **Rare**: Tinnitus

### Cardiac disorders
- **Very rare**: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, (particularly at high doses 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).

### Vascular disorders
- **Very rare**: Arterial hypertension

### Gastrointestinal disorders
- **Common**: Abdominal pain, dyspepsia and nausea. Heartburn
- **Uncommon**: Diarrhoea, flatulence, constipation and vomiting.
- **Very rare**: Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures. Peptic ulcer, perforation or gastrointestinal haemorrhage, melena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn’s disease (see section 4.4).
  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 melena or haematemesis occurs.

### Skin and subcutaneous tissue disorders
- **Uncommon**: Various skin rashes. Hypersensitivity reactions with urticaria and pruritus.
- **Very rare**: Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. 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
4.9 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, dizziness, hypotension and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitement 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 anti-rheumatic products, non-steroids; propionic acid derivative
ATC Code: M01A E01

Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine therefore are the same as those of ibuprofen acid.

Ibuprofen is an NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggests 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 of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane of 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 conclusion 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
Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Peak plasma concentration of ibuprofen occurs 1 - 2 hours after administration of ibuprofen acid.

Peak plasma concentration is achieved within 25 minutes for Nurofen Express Soluble (400mg ibuprofen lysine) compared with 90 minutes (p<0.0001) for 2 x 200mg Nurofen (ibuprofen acid) tablets and 30 minutes (p=0.0441) for 2 x 200 mg Nurofen (ibuprofen lysine) tablets.

The mean plasma concentration 4.5 minutes after dosing with Nurofen Express Soluble was 8.69 μg/ml (SD 3.12; 95%CI 7.40 - 9.98), while at 9 minutes post-dosing the mean plasma concentration was 20.27 μg/ml (SD 7.37; 95%CI 17.23 - 23.32).
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

Elimination half-life is approximately 2 hours.

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

5.3 Preclinical safety data
The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal 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 inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat and mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Betadex
Lemon essence (containing natural flavouring substances and preparations, maltodextrin, modified maize starch and tartrazine E102)
Saccharin sodium (E954),
Sodium cyclamate (E952)
Sodium citrate (E331)
Sucrose

6.2 Incompatibilities
The reconstituted solution should not be mixed with other medicinal products.

6.3 Shelf life
As packaged from date of manufacture: 3 years.

Once the solution is prepared, use immediately.

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack sizes: 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15 and 16 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for reconstitution are included in section 4.2

The appearance of the solution is colourless, clear to translucent with no solid particulates.

7 MARKETING AUTHORITY/IS HOLDER
Reckitt Benckiser Healthcare (UK) Ltd
Dansom Lane
Hull
HU8 7DS
<table>
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<th>MARKETING AUTHORISATION NUMBER(S)</th>
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1 NAME OF THE MEDICINAL PRODUCT
Nurofen Express 400mg Oral Powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains Ibuprofen 400mg (as Ibuprofen lysinate). 

Excipient(s):
Sucrose  1.26g/sachet
Tartrazine  0.0067 mg/sachet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral powder
A white, lemon flavoured powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of mild to moderate pain associated with headache, migraine, backache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms such as sore throat and fever.

4.2 Posology and method of administration
For oral administration and short-term use only.
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 5 days when treating pain and 3 days when treating fever.

Adults, the elderly and children aged over 12 years
Initial dose - one sachet. Then, if necessary, one sachet up to three times a day as required.
Dissolve the contents of the sachet in a glass of water, stir, and then drink immediately.
Leave at least six hours between doses. Do not exceed more than 3 sachets (1200mg) in any 24 hour period.

Special patient groups:
Elderly:
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 insufficiency:
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 insufficiency (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).

Children and adolescents:
Not to be given to children under 12 years of age.

4.3 Contraindications
Patients with a known hypersensitivity to ibuprofen, tartrazine (E102) or any of the constituents in the product.
Patients with a history of bronchospasm, asthma, rhinitis, angioedema or urticaria associated with acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs).
History of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
Patients with severe hepatic failure, severe renal failure or severe heart failure.
In patients with cerebrovascular or other active bleeding.
In patients with coagulation disorders or bleeding diathesis.
In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake). During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

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

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See Section 4.2).

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

Other NSAID’s:
Use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

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

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

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

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

Impaired female fertility:
There is 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 the treatment.

Gastrointestinal:
NSAID’s 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 (GI) bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time 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 and 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 4.5).

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.
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 (SSRIs) or anti-platelet agents such as aspirin (See Section 4.5).

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

**Dermatological:**
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Nurofen Express Soluble 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 tissue 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 Nurofen Express Soluble in case of varicella.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

<table>
<thead>
<tr>
<th>Concomitant use of ibuprofen with:</th>
<th>Possible effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other NSAIDs, including salicylates:</strong></td>
<td>The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).</td>
</tr>
<tr>
<td><strong>Digoxin:</strong></td>
<td>The concomitant use of Nurofen Express Soluble 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).</td>
</tr>
<tr>
<td><strong>Corticosteroids:</strong></td>
<td>Corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal; ulceration or bleeding) (see section 4.3)</td>
</tr>
<tr>
<td><strong>Anti-platelet agents:</strong></td>
<td>Increased risk of gastrointestinal bleeding (see section 4.4).</td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid (low dose):</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Anticoagulants:</strong></td>
<td>NSAIDs may enhance the effect of anti-coagulants, such as warfarin and heparin (see section 4.4). Monitoring of coagulation state is recommended in case of simultaneous treatment.</td>
</tr>
<tr>
<td><strong>Phenytoin:</strong></td>
<td>The concomitant use of Nurofen Express Soluble with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is...</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs):</strong></td>
<td>Increased risk of gastrointestinal bleeding (see section 4.4).</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Lithium:</strong></td>
<td>The concomitant use of Nurofen Express Soluble 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).</td>
</tr>
<tr>
<td><strong>Probenecid and sulfinpyrazone:</strong></td>
<td>Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.</td>
</tr>
<tr>
<td><strong>Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists:</strong></td>
<td>NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. 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 cyclooxygenase 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.</td>
</tr>
<tr>
<td><strong>Potassium sparing diuretics:</strong></td>
<td>The concomitant administration of Nurofen Express Soluble and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).</td>
</tr>
<tr>
<td><strong>Methotrexate:</strong></td>
<td>The administration of Nurofen Express Soluble within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.</td>
</tr>
<tr>
<td><strong>Ciclosporin:</strong></td>
<td>The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.</td>
</tr>
<tr>
<td><strong>Tacrolimus:</strong></td>
<td>The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.</td>
</tr>
<tr>
<td><strong>Zidovudine:</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Sulphonylureas:</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
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. |
| NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone. |

### 4.6 Fertility, pregnancy and lactation

#### Fertility

See section 4.4 regarding female fertility.

#### 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 gastrocsis 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, Nurofen Express should not be given unless clearly necessary. If Nurofen Express 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: cardiopulmonary toxicity (with premature closure of the ductusarteriosus 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, Nurofen Express Soluble 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 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 Nurofen Express Soluble 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

Hypersensitivity reactions have been reported and these may consist of:

Non-specific allergic reactions and anaphylaxis
Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
Various skin reactions e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The following list of adverse effects relates to those experienced with ibuprofen at 400mg per single dose up to 1200mg maximum daily dose, for short term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Please note that within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Frequency Grouping</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Very common (&gt;1/10)&gt;</td>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Common (&gt;1/100 to &lt;1/10)&gt;</td>
<td>Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs. If signs of an infection occur or get worse during use of Nurofen Express Soluble 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. 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.</td>
</tr>
<tr>
<td>Uncommon (&gt;1/1,000 to &lt;1/100)&gt;</td>
<td>Blood and Lymphatic system disorders</td>
</tr>
<tr>
<td>Rare (&gt;1/10,000 to &lt;1/1,000)&gt;</td>
<td>Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.</td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000)&gt;</td>
<td>Immune system disorders</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).</td>
</tr>
<tr>
<td>Very rare</td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Very rare</td>
<td>Psychotic reactions, depression</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Nervous System disorders</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Headache, dizziness, sleeplessness, tinnitus, tiredness, agitation, irritability</td>
</tr>
<tr>
<td>Eye disorder</td>
<td>Very rare</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>common:</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon:</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Very rare:</td>
</tr>
</tbody>
</table>
4.9 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, dizziness, hypotension 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 anti-rheumatic products, non-steroids; propionic acid derivative

ATC Code: M01A E01

Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine therefore are the same as those of ibuprofen acid.

Ibuprofen is an NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggests 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 of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane of 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 conclusion 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

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Peak plasma concentration of ibuprofen occurs 1 - 2 hours after administration of ibuprofen acid.

Peak plasma concentration is achieved within 25 minutes for Nurofen Express Soluble (400mg ibuprofen lysine) compared with 90 minutes (p<0.0001) for 2 x 200mg Nurofen (ibuprofen acid) tablets and 30 minutes (p=0.0441) for 2 x 200 mg Nurofen (ibuprofen lysine) tablets.

The mean plasma concentration 4.5 minutes after dosing with Nurofen Express Soluble was 8.69 μg/ml (SD 3.12; 95%CI 7.40 - 9.98), while at 9 minutes post-dosing the mean plasma concentration was 20.27 μg/ml (SD 7.37; 95%CI 17.23 - 23.32).
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

Elimination half-life is approximately 2 hours.

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

5.3 Preclinical safety data
The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal 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 inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat and mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Betadex
Lemon essence (containing natural flavouring substances and preparations, maltodextrin, modified maize starch and tartrazine E102)
Saccharin sodium (E954),
Sodium cyclamate (E952)
Sodium citrate (E331)
Sucrose

6.2 Incompatibilities
The reconstituted solution should not be mixed with other medicinal products.

6.3 Shelf life
As packaged from date of manufacture: 3 years.
Once the solution is prepared, use immediately.

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack sizes: 1, 2, 3, 4, 5, 6, 7 and 8 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.
Instructions for reconstitution are included in section 4.2
The appearance of the solution is colourless, clear to translucent with no solid particulates.

7 MARKETING AUTHORISATION HOLDER
Reckitt Benckiser Healthcare (UK) Ltd
Dansom Lane
Hull
HU8 7DS

8 MARKETING AUTHORISATION NUMBER(S)
PL 00063/0616

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/11/2011

10 DATE OF REVISION OF THE TEXT
28/11/2011
Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nurofen Express Soluble 400mg Oral Powder Ibuprofen

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

- This medicine is available without prescription. However, you still need to take Nurofen Express carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not get better after 5 days when taking pain or 3 days when treating fever.
- 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 Nurofen Express is and what it is used for
2. Before you take Nurofen Express
3. How to take Nurofen Express
4. Possible side effects
5. How to store Nurofen Express
6. Further Information

1. WHAT Nurofen EXPRESS IS AND WHAT IT IS USED FOR

Nurofen Express contains ibuprofen 400mg as ibuprofen base. Ibuprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). These medicines provide relief by changing the body's response to pain, swelling and high temperature.

Nurofen Express is used to relieve:
- symptoms of mild to moderate pain such as headache, toothache, period pains, rheumatic and muscular pain and migraine
- cold and flu symptoms such as sore throat and fever

2. BEFORE YOU TAKE NUROFEN EXPRESS

Do not take Nurofen Express if you:
- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding of the stomach
- are allergic to ibuprofen, tartrazine (E102) or any of the other ingredients (see section 6) of Nurofen Express or to acetylsalicylic acid (aspirin) or other anti-inflammatory painkillers
- suffer from severe kidney, liver or heart problems
- have had gastrointestinal bleeding or perforation when previously taking ibuprofen, acetylsalicylic acid (aspirin) or other similar painkillers (NSAIDs)
- are taking Anti-Inflammatory drugs
- have ever suffered from shortness of breath, have had asthma, skin rash, itchy runny nose or facial swelling when previously taking ibuprofen, acetylsalicylic acid (aspirin) or other similar painkillers (NSAIDs)
- are suffering from severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- are suffering from cerebrovascular or other active bleeding
- are suffering from blood cell production or clotting disorders
- are in the last three months of pregnancy (see below)

Please do not give children under 12 years of age. Speak to a pharmacist or your doctor before taking this product if you:

Other warnings:
- Medicines such as Nurofen Express may be associated with a small increased risk of heart attack or stroke. Any risk is more likely with those who have had a stroke or think that they might be at risk of these conditions (for example if you have high blood pressure, diabetes, high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist.
- Taking a painkiller for headaches for too long can make them worse.

Fertility, pregnancy and breast-feeding

Do not take in the last 3 months of pregnancy. Speak to your doctor or pharmacist before taking this product if you are in the first 6 months of pregnancy or are breast-feeding.

This medicine passes into breast milk but may be used during breast-feeding if it is used at the recommended dose and for the shortest possible time.

Nurofen Express belongs to a group of medicines which may impair fertility in women. It is reversible on stopping the medicine. It is unlikely that Nurofen Express, used occasionally, will affect your chance of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

Driving and using machines

For short-term use and at normal dosage this medicine has no or negligible influence on the ability to drive and use machines. If side-effects such as tiredness or dizziness occur do not drive or operate machines. Alcohol consumption increases the risk of these side-effect.

Important information about some of the ingredients of Nurofen Express

Nurofen Express contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Nurofen Express contains tartrazine (E102). This may cause allergic reactions.

3. HOW TO TAKE NUROFEN EXPRESS

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

Always take Nurofen Express Oral Powder exactly as stated in this package leaflet. You should check with your doctor or pharmacist if you are not sure. The standard dose is:

Adults and children aged 12 years and older:
For oral use after dissolving in water. Dissolve the content of one sachet in a glass of water, stir and then drink immediately. You can take one sachet up to three times a day as required. Leave at least six hours between doses. Do not take more than three sachets in any 24 hour period.

Not to be given to children under 12 years of age.
You should not take Nurofen Express for longer than 5 days when treating pain and 3 days when treating fever unless your doctor tells you to. If symptoms persist or worsen consult your doctor.

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 more Nurofen Express than you should
Consult a doctor immediately. The following signs may occur:
- nausea, vomiting, stomach pain, headache, dizziness,
- drowsiness, tinnitus, blurred vision, ringing in the ears.
- Rarely: low blood pressure and loss of consciousness.

If you have any further questions on the use of this product, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Nurofen Express 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. Although side effects are uncommon, you may suffer one of the known side effects of NSAIDs: 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:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

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, blood in your faeces (stools/motions), vomiting blood or dark particles that look like coffee grounds.
- **signs of very rare but serious allergic reaction** such as: worsening of asthma, unexplained wheezing or shortness 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**
- heart burn, abdominal pain, feeling sick and indigestion,

**Uncommon**
- inflammation of the stomach, worsening of colitis and Crohn's disease
- headache, dizziness, sleeplessness, agitation, irritability or tiredness
- visual disturbances
- flatulence (wind), diarrhoea, constipation and vomiting
- allergic reactions, such as skin rashes, itching and asthma attacks

**Rare**
- tinnitus (ringing in the ears)
- kidney damage and the development of gout

**Very rare**
- inflammation of the oesophagus or pancreas, blockages in the gut
- serious infections of the skin have occurred during chicken pox
- kidney disorders that may be shown by passing less or more urine than normal, cloudy urine, blood in the urine,

Consult a doctor before using Nurofen Express if any above mentioned conditions concern you.

Taking other medicines

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

- blood thinning or anti-clotting medicines (anticoagulants) such as acetylsalicylic acid (aspirin), warfarin, tricopine
- glucocorticoids (medicinal products containing cortisone or cortisone-like substances), aspirin, or other NSAIDs (anti-inflammatory and analgesics): since these may increase the risk of gastrointestinal ulcers or bleeding
- lithium (a medicine for manic depressive illness and depression) since the effect of lithium may be enhanced
- selective serotonin reuptake inhibitors (a medicine used for depression) as these may increase the risk of gastrointestinal side effects.
- methotrexate (a medicine for cancer or rheumatism) since the effect of methotrexate may be enhanced
- zidovudine: (a medicine for treating HIV infection) since the use of Nurofen Express may result in an increased risk of bleeding into a joint or a bleeding that leads to swelling.
- ciclosporin and tacrolimus (to prevent transplant rejection) as there could be an increased risk for the kidney.
- medicines for high blood pressure (ACE-inhibitors e.g. captopril, betareceptor blocking medicines, angiotensin II antagonists) and water tablets (diuretics), as NSAIDs may reduce the effects of these medicines and there could be a possible increased risk for the kidney (using potassium sparing diuretics with ibuprofen can lead to high blood levels of potassium)
- sulfonylureas (antidiabetic medicine) as interactions may be possible
- phenytin (for epilepsy) as the effect may be enhanced
- quinolone antibiotics as the risk of convulsions may be increased.
- cardiac glycosides such as digoxin
- mifepristone (used to terminate pregnancies) as the effect may be reduced
- probenecid and sulfpyrazone (medicines for gout); it may take longer for ibuprofen to be broken down by the body.
Nurofen Express 400mg Oral Powder

5. HOW TO STORE Nurofen® EXPRESS

Keep out of the reach and sight of children.

This medicinal product does not require any special temperature storage conditions.

Do not use Nurofen® Express after the expiry date which is stated on the carton and sachets. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Nurofen® Express contains: Each sachet contains 400mg of the active substance ibuprofen (as ibuprofen lysinate).

The other ingredients are:
- Ibuprofen
- Sodium saccharate (E954)
- Sodium cyclamate (E952)
- Sodium citrate (E331)
- Sorbitol
- Lemon essence (containing natural flavouring substances and preservatives, maltodextrin, modified maize starch and ferric ferrocyanide E152)

What Nurofen® Express looks like and contents of the pack:
This medicine is a white, lemon flavoured powder supplied in sachets.

Outer carton containing 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15 and 16 sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Reckitt Benckiser Healthcare (UK) Ltd, HUB 7DS.
PL 00653/0611

Manufacturer
Laboratorios de aplicaciones farmacodinámicas, s.a. (farm)
Granvia, 16
08025 BARCELONA (SPAIN)

This medicinal product is authorised in the Member States of the EEA under the following names:

- Czech Republic: Nurofen Rapid 400mg peroralní prášek
- Hungary: Nurofen Rapid Forte por bérlőjég oktatózó
- Netherlands: Nurofen Express 40 mg. poeder voor oplossing
- Poland: Nurofen Ultra Forte rozpuszczalny
- Republic of Ireland: Nurofen Express 400mg soluble powder
- Romania: Nurofen Express 400 mg Solubil pabere
- Slovakia: Nurofen Rapid 400mg peroralní prášek
- United Kingdom: Nurofen Express Soluble 400mg oral powder

This leaflet was last approved in September 2011.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Nurofen® Express 400mg Oral Powder
Ibuprofen

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

- This medicine is available without prescription. However, you still need to take Nurofen® Express carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 5 days when treating pain or 3 days when treating fever.
- 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 Nurofen® Express is and what it is used for
2. Before you take Nurofen® Express
3. How to take Nurofen® Express
4. Possible side effects
5. How to store Nurofen® Express
6. Further information

1. WHAT NUROFEN® EXPRESS IS AND WHAT IT IS USED FOR

Nurofen® Express contains ibuprofen 400mg as ibuprofen lysinate. Ibuprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). These medicines provide relief by changing the body’s response to pain, swelling and high temperature.

Nurofen® Express is used to relieve:
- symptoms of mild to moderate pain such as headache, toothache, period pains, rheumatic and muscular pain and migraine.
- cold and flu symptoms such as sore throat and fever.

2. BEFORE YOU TAKE NUROFEN® EXPRESS

Do not take Nurofen® Express if you:
- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding of the stomach
- are allergic to ibuprofen, tartrazine (E102) or any of the other ingredients (see section 6) of Nurofen Express or to acetylsalicylic acid (aspirin) or other anti-inflammatory painkillers
- suffer from severe kidney, liver or heart problems
- have had gastrointestinal bleeding or perforation when previously taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
- have ever suffered from shortness of breath, have had a worsening of asthma, skin rash, itchy runny nose or facial swelling when previously taking ibuprofen, acetylsalicylic acid (aspirin) or other similar painkillers (NSAIDs)
- are suffering from cerebrovascular or other active bleeding
- are suffering from blood cell production or clotting disorders
- are in the last three months of pregnancy (see below).

Please do not give to children under 12 years of age. Speak to a pharmacist or your doctor before taking this product if you:

Other warnings
- Medicines such as Nurofen Express may be associated with a small increased risk of heart attack or stroke. Any risk is more likely with high doses and prolonged treatment. If you have heart problems, have had a stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes, high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist.
- Taking a painkiller for headaches for too long can make them worse.

Fertility, pregnancy and breast-feeding
Do not take in the last 3 months of pregnancy. Speak to your doctor or pharmacist before taking this product if you are in the first 6 months of pregnancy or are breast-feeding.

This medicine passes into breast milk but may be used during breast-feeding if it is used at the recommended dose and for the shortest possible time.

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

Driving and using machines
For short-term use and at normal dosage this medicine has no or negligible influence on the ability to drive and use machines. If side-effects such as tiredness or dizziness occur do not drive or operate machines. Alcohol consumption increases the risk of these side-effect.

Important information about some of the ingredients of Nurofen® Express.
Nurofen Express contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Nurofen Express contains tartrazine (E102). This may cause allergic reactions.

3. HOW TO TAKE NUROFEN® EXPRESS

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

Always take Nurofen® Express exactly as stated in this package leaflet. You should check with your doctor or pharmacist if you are not sure. The standard dose is:

Adults and children aged 12 years and older:
For oral use after dissolving in water.
Dissolve the content of one sachet in a glass of water, stir, then drink immediately.
You can take one sachet up to three times a day as required. Leave at least six hours between doses.
Do not take more than three sachets in any 24 hour period.

Not to be given to children under 12 years of age.
You should not take Nurofen Express for longer than 5 days when treating pain and 3 days when treating fever unless your doctor tells you to. If symptoms persist or worsen consult your doctor.

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 more Nurofen® Express than you should
Consult a doctor immediately. The following signs may occur:
Nausea, vomiting, stomach pain, headache, dizziness, drowsiness, dizziness, blurred vision, ringing in the ear.
Rarely: low blood pressure and loss of consciousness.
If you have any further questions on the use of this product, ask your doctor or pharmacist.
DCPAR Nurofen Express Soluble 400mg Oral Powder
Nurofen Express 400mg Oral Powder

1. have or have had asthma
2. have kidney, heart, liver or bowel problems
3. have high blood pressure, diabetes, high cholesterol or are a smoker
4. have been told by your doctor that you have an intolerance to some sugars
5. have systemic lupus erythematosus (a condition of the immune system causing joint pain, skin changes and other organ disorders)
6. have had a heart attack or stroke
7. have a history of gastrointestinal disease (such as ulcerative colitis or Crohn’s disease)
8. are in the first 6 months of pregnancy
9. have chicken pox (varicella).

Consult a doctor before using Nurofen Express if any above mentioned conditions concerns you.

Taking other medicines

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

- blood thinning or anti-clotting medicines (anticoagulants) such as acetylsalicylic acid (aspirin), warfarin, ticlopidine,
- glucocorticoids (medicinal products containing cortisone or cortisone-like substances), aspirin, or other NSAIDs (anti-inflammatories and analgesics): since these may increase the risk of gastrointestinal ulcers or bleeding
- lithium (a medicine for manic depressive illness and depression) since the effect of lithium may be enhanced
- selective serotonin reuptake inhibitors (a medicine used for depression) as these may increase the risk of gastrointestinal side effects.
- methotrexate (a medicine for cancer or rheumatism) since the effect of methotrexate may be enhanced
- zidovudine: (a medicine for treating HIV infection) since the use of Nurofen Express may result in an increased risk of bleeding into a joint or a bleeding that leads to swelling.
- ciclosporin and tacrolimus (to prevent transplant rejection) as there could be an increased risk for the kidney.
- medicines for high blood pressure (ACE-inhibitors e.g. captopril, betablocker blocking medicines, angiotensin II antagonists) and water tablets (diuretics), as NSAIDs may reduce the effects of these medicines and there could be a possible increased risk for the kidney (using potassium sparing diuretics with ibuprofen can lead to high blood levels of potassium)
- sulfonylureas (antiabetic medicine) as interactions may be possible
- phenytoin (for epilepsy) as the effect may be enhanced
- quinolone antibiotics as the risk of convulsions may be increased.
- cardiac glycosides such as digoxin
- mifepristone (used to terminate pregnancies) as the effect may be reduced
- probenecid and sulfipyrazone (medicines for gout): it may take longer for ibuprofen to be broken down by the body.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nurofen Express 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. Although side effects are uncommon, you may suffer one of the known side effects of NSAIDs. 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>Side Effect 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 known:</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, blood in your faeces (stools/motions), vomiting blood or dark particles that look like coffee grounds.
- signs of rare but serious allergic reaction such as worsening of asthma, unexplained wheezing or shortness 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
- heart burn, abdominal pain, feeling sick and indigestion

Uncommon
- inflammation of the stomach, worsening of colitis and Crohn’s disease
- headache, dizziness, sleeplessness, agitation, irritability or tiredness
- visual disturbances
- flatulence (wind), diarrhoea, constipation and vomiting
- allergic reactions, such as skin rashes, itching and asthma attacks

Rare
- tinnitus (ringing in the ears)
- kidney damage and the development of gout

Very rare
- inflammation of the oesophagus or pancreas, blockages in the gut
- serious infections of the skin have occurred during chicken pox
- kidney disorders that may be shown by passing less or more urine than normal, cloudy urine, blood in the urine, pain in the back and/or swelling (particularly of the legs).

RB004517
In general, the habitual use of (several sorts of) analgesics can lead in rare cases to lasting severe kidney problems.

- blood disorders resulting in unexplained or unusual bruising or bleeding, fever, sore throat, mouth ulcers, flu-like symptoms and severe exhaustion
- psychotic reactions and depression
- worsening of inflammation due to infection
- high blood pressure, arterial hypertension, palpitations, heart failure, heart attack
- liver problems or inflammation of the liver, liver failure or damage, particularly in long-term use, shown by yellowing of the skin and eyes or pale stools and dark urine.
- 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.

swelling of skin tissue such as hands, feet or face.

Medicines such as Nurofen Express may be associated with a small increased risk of heart attack (‘myocardial infarction’) or stroke.

If any of the side effects get serious, or if you notice any side effects not listed in the leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NUROFEN EXPRESS

Keep out of the reach and sight of children.

This medicinal product does not require any special temperature storage conditions.

Do not use Nurofen Express after the expiry date which is stated on the carton and sachet. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Nurofen Express contains:
Each sachet contains 400mg of the active substance ibuprofen (as ibuprofen lysinate).

The other ingredients are:
Betadex
Lemon essence (containing natural flavouring substances and preparations, maltodextrin, modified maize starch and tartrazine E102)
Saccharin sodium (E954)
Sodium cydamate (E952)
Sodium citrate (E331)
Sucrose

What Nurofen Express looks like and contents of the pack:
This medicine is a white, lemon flavoured powder supplied in sachets.
Outer carton containing 1, 2, 3, 4, 5, 6, 7 and 8 sachets.
Not all pack sizes may be marketed.[P]

Marketing Authorisation Holder
Reckitt Benckiser Healthcare (UK) Ltd, HUR 7DS.
PL 00003/0616

Manufacturer
Laboratorio de aplicaciones farmacodinámicas, s.a. (facli)
Grassot, 16
08025 BARCELONA (SPAIN)

This medicinal product is authorised in the Member States of the EEA under the following names:

<table>
<thead>
<tr>
<th>Country</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>Nurofen Ultra Forte do rozpuszczania</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Nurofen Express 400mg oral powder</td>
</tr>
</tbody>
</table>

This leaflet was last approved in November 2011.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Nurofen Express Soluble 400mg Oral Powder/Nurofen Express 400mg Oral Powder (PL 00063/0611 & 0616; UK/H/3534 & 3996/001/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and the following as concerned member states (CMS):

- UK/H/3534/001/DC: The Czech Republic (CZ), Hungary (HU), Ireland (IE), the Netherlands (NL), Poland (PL), Romania (RO) and the Slovak Republic (SK)
- UK/H/3996/001/DC: Poland (PL)

The products are supplied through pharmacies (P) and are indicated for the relief of mild to moderate pain associated with headache, migraine, backache, period pain, dental pain, rheumatic and muscular pain, cold and flu symptoms such as sore throat and fever.

These are applications made under the decentralised procedure, according to Article 8.3 of 2001/83/EC, as amended, for a known active substance, ibuprofen lysinate. These applications concern line extension applications to Nurofen 200mg Tablets, first authorised to Crookes Healthcare Limited on 15th July 2003 (PL 00327/0146). This licence has since undergone a change of ownership to Reckitt Benckiser Healthcare (UK) Limited on 29th January 2011 (PL 00063/0385).

Ibuprofen lysinate is the lysine salt of ibuprofen and following oral administration dissociates to ibuprofen and lysine. Ibuprofen lysinate tablets are already marketed in the Community, for example as Nurofen Maximum Strength Migraine Pain 684mg in the UK (equivalent to 400mg ibuprofen).

Ibuprofen was originally introduced in the late 1960s as a prescription only medicine and became available over the counter in 1983 in the UK. Ibuprofen inhibits prostaglandin synthesis by competitive inhibition of the two isomers of cyclooxygenase, COX-1 and COX-2. It is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of ibuprofen lysinate is well-established. The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for non-submission of a Risk Management Plan.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 21st September 2011. After a subsequent national phase, the licences were granted in the UK on 28th November 2011.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Nurofen Express Soluble 400mg Oral Powder  
Nurofen Express 400mg Oral Powder |
| Name(s) of the active substance(s) (INN) | Ibuprofen Lysinate |
| Pharmacotherapeutic classification (ATC code) | Anti-inflammatory and anti-rheumatic products, non-steroids; propionic acid derivative  
ATC Code: (M01A E01) |
| Pharmaceutical form and strength(s) | 400mg oral powder |
| Reference numbers for the Decentralised Procedure | UK/H/3534/001/DC  
UK/H/3996/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/3534/001/DC: The Czech Republic (CZ), Hungary (HU), Ireland (IE), the Netherlands (NL), Poland (PL), Romania (RO) and the Slovak Republic (SK)  
UK/H/3996/001/DC: Poland (PL) |
| Marketing Authorisation Number(s) | PL 00063/0611  
PL 00063/0616 |
| Name and address of the authorisation holder | Reckitt Benckiser Healthcare (UK) Ltd  
Dansom Lane  
Hull  
HU8 7DS |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substances

INN/Ph.Eur name: Ibuprofen D, L-lysine
Chemical Name: (2RS)-2-[4-(2-methylpropyl) phenyl] propanoic acid compound with (2R,S)-2,6-diamino-hexanoic acid Lysine, mono[a-methyl-4-(2-methylpropyl) benzeneacetate]

2-(4-Isobutyl-phenyl)-propionic acid; compound with 2,6-diamino-hexanoic acid α-methyl-4-(2-methylpropyl)-benzene-acetic acid 2,6-diamino-hexanoic acid salt

Molecular Formula: C_{19}H_{32}N_{2}O_{4}
Structural Formula:

Solubility: Freely soluble in water, sparingly soluble in methanol, very slightly soluble in ethanol and practically insoluble in acetone, ether, methylene chloride, ethyl acetate and dimethylformamide.

Molecular Weight: 352.47

Ibuprofen D, L-lysine is a raceme mixture of ibuprofen lysine salt, obtained using a raceme 50% aqueous solution of D, L-lysine and ibuprofen.

Ibuprofen D, L-lysine complies with in-house specifications.

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 specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is 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 specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines.
Stability studies have been performed with the drug substance and no significant changes of the parameters were observed. On the basis of the results, the RMS agreed that a suitable re-test period could be approved.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients in the powder consist of the pharmaceutical excipients betadex, lemon essence (containing natural flavouring substances and preparations, maltodextrin, modified maize starch and tartrazine E102), saccharin sodium (E954), sodium cyclamate (E952), sodium citrate (E331) and sucrose.

With the exception of lemon essence, all excipients comply with their respective European Pharmacopoeia monographs. Lemon essence complies with the in-house specifications.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical Development**

The proposed ibuprofen D, L-lysine oral powder is developed to be an oral powder for rapid reconstitution with water for administration. The pharmaceutical development was focused on creating a homogeneous powder.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches have been provided and are satisfactory.

**Finished Product Specification**

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

**Container-Closure System**

These products are packaged in single dose sachets made of a heat-sealable paper, aluminium sheet and polythene complex which are further packaged in out cardboard cartons.

Pack sizes are:
PL 00063/0611: 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15 and 16 sachets.
PL 00063/0616: 1, 2, 3, 4, 5, 6, 7 and 8 sachets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.
Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years as packaged from the date of manufacture. Once the solution is prepared, it should be used immediately. This medicinal product does not require any special temperature storage conditions. This is satisfactory.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels
The SmPCs, PILs and labelling are pharmaceutically acceptable. The UK approved PIL and label text are included in modules 3 and 4 of this report.

User testing results for the PILs for these products have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of ibuprofen D, L-lysine are well-known. As ibuprofen D, L-lysine is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is appropriate.

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

A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

It is recommended that Marketing Authorisations are granted for these applications from a non-clinical point of view.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
The clinical pharmacology of ibuprofen is well-known. Ibuprofen salts such as those of sodium and lysine are more water soluble than ibuprofen acid and are therefore expected to show a faster absorption. This may have clinical benefit. Lysine is a naturally occurring amino acid with no significant pharmacological activity in the amounts present. Once absorbed, the distribution, metabolism and excretion of ibuprofen from lysinate is expected to be similar to that from ibuprofen acid.

As well as the submitted bioequivalence study, the applicant has also described a study of the proposed product by Fardi (IBU-1999/006, 1999). This was a comparative bioavailability study of 200mg, 400 mg and 600mg doses, compared to an effervescent formulation of 600mg ibuprofen acid. Bioequivalence was established for AUC, but $C_{\text{max}}$ was higher and $T_{\text{max}}$ shorter for the lysinate formulation. A summary was provided of the results of pharmacokinetic studies carried out with ibuprofen lysine tablets that show faster rate of absorption but comparable exposure compared to conventional ibuprofen acid tablets.

**Pharmacokinetics**

*A randomised, single-dose, 3-way crossover, open label study to compare the pharmacokinetics of the test product Nurofen Express Oral Powder (2x200mg sachets) versus the reference product Nurofen Tablets (2x200mg) versus the comparator product Ibuprofen Lysine Tablets (2x200mg) in healthy subjects under fasted conditions.*

Test product (T): 2x200mg sachets of Nurofen Express Oral Powder (ibuprofen lysinate).

Reference product (R): 2x200mg Nurofen Tablets (ibuprofen) first authorised to Crookes Healthcare Limited on 15th July 2003 (PL 00327/0146). This licence has since undergone a change of ownership to Reckitt Benckiser Healthcare (UK) Limited on 29th January 2011 (PL 00063/0385).

Comparator product (C): 2x200mg Nurofen Express Caplets (ibuprofen lysine) first authorised to Crookes Healthcare Limited on 27th July 2000 (PL 00327/0125). This licence has since undergone a change of ownership to Reckitt Benckiser Healthcare (UK) Limited on 29th April 2011 (PL 00063/0380).

Blood samples were taken pre- and up to 720 minutes post dose. There was a washout period of at least 3-7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.
Results for ibuprofen are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) (ug/mL.h)</th>
<th>(\text{AUC}_{0-\infty}) (ug/mL.h)</th>
<th>(\text{C}_{\text{max}}) (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>117.31</td>
<td>119.36</td>
<td>45.83</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>122.88</td>
<td>125.55</td>
<td>35.30</td>
</tr>
<tr>
<td>Comparator (C)</td>
<td>119.20</td>
<td>121.25</td>
<td>45.92</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>95.46 – 92.56</td>
<td>95.07 – 92.17 – 98.06</td>
<td>129.81 – 122.04 – 138.08</td>
</tr>
<tr>
<td>T/C Ratio (90% CI)</td>
<td>95.41 – 101.51</td>
<td>98.44 – 95.42 – 101.55</td>
<td>99.80 – 93.79 – 106.18</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/comparator ratio of geometric means for \(\text{AUC}_{0-t}\), \(\text{AUC}_{0-\infty}\) and \(\text{C}_{\text{max}}\) for ibuprofen lie within the acceptance criteria of 80-125%.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for \(\text{AUC}_{0-t}\) and \(\text{AUC}_{0-\infty}\) for ibuprofen lie within the acceptance criteria of 80-125%. The 90% confidence intervals test/reference ratio of geometric mean for \(\text{C}_{\text{max}}\) fell outside the acceptance criteria of 80-125%.

This showed that the rate of absorption of ibuprofen was significantly faster for the test product compared to the reference. This was expected as ibuprofen is known to be absorbed faster from ibuprofen lysine (salt) containing products than standard ibuprofen containing products. Although ibuprofen from ibuprofen lysine is absorbed significantly faster than from ibuprofen acid tablets, the distribution, metabolism and excretion of ibuprofen will be the same for either formulation.

The 90% confidence intervals test/reference ratio of geometric mean for \(\text{C}_{\text{max}}\) falling outside the acceptance criteria was considered minor and unlikely to affect the pharmacokinetic conclusions, as the test product was shown to be bioequivalent to the approved comparator product.

Thus, bioequivalence has been demonstrated between the test product, Nurofen Express 400mg Oral Powder and comparator product, 2x200mg Nurofen Express Caplets in this study.

The test product, Nurofen Express 400mg Oral Powder is considered bioequivalent with the reference product, 2x200mg Nurofen Tablets for extent of exposure only.

**CLINICAL EFFICACY**

Over 1500 trials have been carried out with ibuprofen formulations. The evidence for the efficacy of ibuprofen in the claimed indications has been adequately summarised. The published data in support of the analgesic efficacy of oral tablet formulations of ibuprofen lysine has also been summarised, as shown in the following table:
The Nelson (1994) study showed ibuprofen lysine 200mg tablet to be a more effective analgesic than aspirin 500mg tablet for post-operative dental pain. The onset of significant analgesia was within 30 minutes and lasted 6 hours. In a study by Mehlisch et al (1995), ibuprofen lysine tablets 400mg were more effective than paracetamol 1000mg in the relief of post-operative dental pain. Wahl et al (1997) showed ibuprofen lysine to be more effective than a combination of paracetamol 200mg, aspirin 250mg and caffeine 50mg for the relief of post-operative dental pain. Siebel (2004) used a laser algesimetry study to show that ibuprofen lysine 400mg was superior to ibuprofen acid 400mg with respect to the onset and extent of analgesia.

**CLINICAL SAFETY**

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

The adverse drug reactions of ibuprofen are well-known. Lysine is a naturally occurring amino acid known to be non-toxic in pharmaceutical oral formulations at therapeutic doses.

The proposed formulation of ibuprofen lysine powder 400mg has been used in 2 clinical studies. In the Fardi study discussed in the Clinical Pharmacology Section, the adverse events were mild. 3 patients experienced diarrhoea following administration of ibuprofen lysinate 1025mg (equivalent to 600mg ibuprofen acid). The cases were assessed as mild and of probable or definite causality.
Ten further studies were also identified where ibuprofen lysine formulations were used either in single or multiple doses. The adverse events reported were of a similar nature to those reported with ibuprofen acid. It is also discussed that a higher C\text{max} is not expected to be associated with a higher incidence of adverse events, given the wide therapeutic window of ibuprofen, and bioequivalence with marketed ibuprofen lysine products that have not demonstrated additional safety concerns.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are clinically satisfactory.

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

MAA FORM
The MAA form is clinically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications from a clinical point of view.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Nurofen Express Soluble 400mg Oral Powder/Nurofen Express 400mg Oral Powder 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 risk-benefit balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. An overview based on literature review is appropriate.

EFFICACY/SAFETY
Bioequivalence has been demonstrated between the test product, Nurofen Express 400mg Oral Powder and comparator product, 2x200mg Nurofen Express Caplets in this study.

The test product, Nurofen Express 400mg Oral Powder is considered bioequivalent with the reference product, 2x200mg Nurofen Tablets for extent of exposure only.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable. An adequate review of published clinical data has been provided and bioequivalence has been demonstrated.

Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.