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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted STD Chemicals Ltd, a Marketing Authorisation for the medicinal product, Ibuprofen 100 mg/5 mL Oral Suspension (PL 36390/0042) on 2 September 2011. This is a prescription-only medicine.

Ibuprofen oral suspension contains 100 mg of the active ingredient, ibuprofen, in 5 mL. Ibuprofen belongs to a group of drugs called non-steroidal anti-inflammatory drugs (also known as NSAIDS), which relieve pain and reduce inflammation.

Ibuprofen suspension is used to treat conditions affecting the joints and muscles such as:
- swollen joints
- frozen shoulder
- low back pain
- rheumatoid arthritis (including juvenile rheumatoid arthritis or Still’s disease
- ankylosing spondylitis (inflammation of the spine)
- osteoarthritis
- other disorders of the muscles, bones and tendons

Ibuprofen suspension can also be used:
- in soft tissue injuries such as sprains and strains
- to relieve mild to moderate pain in dysmenorrhoea (period pain), dental pain and pain after an operation
- to relieve mild to moderate pain due to headache; including migraine headache
- for short term treatment of pyrexia (fever) in children over one year of age

This application is considered to be identical to a previously granted licence for Ibuprofen 100 mg/5 mL Oral Suspension (PL 08137/0089) on 5th February 2004 to NeoLab Ltd. Holder.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ibuprofen 100 mg/5 mL Oral Suspension (PL 36390/0042) outweigh the risks; hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

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Clinical assessment ......................................... Page 9
Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted STD Chemicals Ltd., a Marketing Authorisation for the medicinal product, Ibuprofen 100 mg/5 mL Oral Suspension (PL 36390/0042), on 2 September 2011. The product is a POM licensed medicine.

This is a simple, abridged, ‘informed consent’ application submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisation for Ibuprofen 100 mg/5 mL Oral Suspension (PL 08137/0089), licensed to Neolab Ltd on 5 February 2004. The reference product cross-refers to the innovator product Brufen 100 mg/5 mL Syrup which was originally granted in the UK to Boots Limited (PL 00014/0217) in 1978. The ownership of this licence changed to Knoll Pharma Limited in April 1993, as PL 13530/0004, to Knoll Limited in July 1995, as PL 00169/0048 and finally to the current MAH, Abbott Laboratories (PL 00037/0339) in February 2002. The innovator product has been authorised in the EEA for over 10 years.

Ibuprofen is a propionic acid derivative [2-(4-isobutylphenyl) propionic acid], non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic activity.

Ibuprofen Oral Suspension is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies, in the treatment of non-articular rheumatic conditions, such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low back pain; in soft tissue injuries such as sprains and strains.

Ibuprofen Oral Suspension is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for symptomatic relief of headache; including migraine headache.

No new data were submitted nor were they necessary for this simple application, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.
1. INTRODUCTION
This is a simple, informed consent application for Ibuprofen 100 mg/5 mL Oral Suspension submitted under Article 10c of Directive 2001/83/EC. The proposed Marketing Authorisation Holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK.

The application cross-refers to Ibuprofen 100 mg/5 mL Oral Suspension (PL 08137/0089) authorised to Neolab Ltd since 5 February 2004. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name
The proposed name of the product is for Ibuprofen 100 mg/5 mL Oral Suspension. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Ibuprofen 100 mg/5 mL Oral Suspension contains the active ingredient, ibuprofen, equivalent to 2.0% w/v. The medicinal product is licensed for marketing in amber-coloured polyethylene terephthalate (PET) bottle containing 500 ml Ibuprofen Oral Suspension sealed with a polypropylene, tamper-evident child resistant cap fitted with a low density polyethylene liner. The bottle is packaged with the Patient Information Leaflet (PIL) into cardboard outer carton.

The approved shelf-life (24 months) and storage conditions (Do not store above 25°C and Keep container in the outer carton and protect from light) are identical to the details registered for the cross-reference product.

2.3 Legal status
This product is a prescription-only medicine.

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation Holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK

The Quality Person (QP) responsible for pharmacovigilance is stated and their curriculum vita has been included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. This is consistent with the cross-reference product.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product (white-coloured, orange-flavoured oral suspension) is identical to that of the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/CARTON
PIL
The PIL is satisfactory and in line with the approved SmPC and has been prepared in the user-tested format.

To support the proposed patient leaflet, a user testing report has been provided for the approved reference product, Ibuprofen 100 mg/5 mL Oral Solution (PL 08137/0089) authorised to Neolab Ltd. The patient leaflet for the reference product met all criteria for successful user testing. The proposed layout and content of the proposed patient leaflet is identical to that of the approved reference product. As a result, bridging justification is accepted for the proposed product without the need for further user testing.

Carton and label
Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference product and complies with
statutory requirements. In line with current legislation the applicant has included the name of the product in Braille on the outer packaging.

7. CONCLUSIONS
The data submitted with this application is acceptable. A Marketing Authorisation was, therefore, granted.
NON-CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10c of EC Directive 2001/83 (as amended). This application is identical to the reference product Ibuprofen 100 mg/5 mL Oral Suspension (PL 08137/0089) authorised to Neolab Ltd on 5 February 2004 in the UK, therefore, no new non-clinical data has been supplied with this application and none are required. A non-clinical overview report has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The marketing authorisation holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As this application is identical to an already authorised reference product, it is not expected that the environmental exposure to ibuprofen will increase following the marketing approval of the proposed product.
**CLINICAL ASSESSMENT**

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to Ibuprofen 100 mg/5 mL Oral Suspension (PL 08137/0089) authorised to Neolab Ltd on 5 February 2004 in the UK.

No new clinical data has been supplied with this application and none are required. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

The marketing authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As this application is identical to an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the MAH 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.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with those previously assessed for the cross-reference product and as such has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
This application is considered identical to the previously granted licence for Ibuprofen 100 mg/5 ml Oral Suspension (PL 08137/0089) authorised to Neolab Ltd on 5 February 2004 in the UK.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory, and consistent with those for the cross-reference product.

A user testing report has been provided for the approved reference product, Ibuprofen 100 mg/5 ml Oral Solution (PL 08137/0089). The patient leaflet for the reference product met all criteria for successful user testing. The proposed layout and content of the proposed patient leaflet is identical to that of the approved reference product. As a result, bridging justification is accepted for the proposed product without the need for further user testing.

Mock-ups of the labeling have been provided and are satisfactory. The approved labeling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging. The MAH has committed to submitting mock-ups for currently mock-ups for currently unmarketed packs to the UK regulatory authority for approval before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. The risk benefit is, therefore, considered to be positive.
**IBUPROFEN 100 MG/5 ML ORAL SUSPENSION**  
**PL 36390/0042**

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 11 February 2011.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 18 February 2011.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 18 May 2011, and 26 July 2011.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 7 July 2011 and 5 August 2011.</td>
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<td>5</td>
<td>The application was determined on 2 September 2011.</td>
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## STEPS TAKEN AFTER ASSESSMENT

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IBUPROFEN 100 MG/5 ML ORAL SUSPENSION
PL 36390/0042

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Ibuprofen 100 mg/5 mL Oral suspension (PL 36390/0042) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Ibuprofen 100 mg/5ml Oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ibuprofen 100 mg/5 ml (equivalent to 2.0% w/v)

Excipients per 5 ml of suspension: liquid maltitol (E965) 1375 mg, sodium methyl parahydroxybenzoate (E219) 8.60 mg, sodium propyl parahydroxybenzoate (E217) 2.25 mg and sodium 0.48 mmol. See section 4.4 for further information.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral suspension.

White-coloured, orange-flavoured oral suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ibuprofen Oral Suspension is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, Ibuprofen Oral Suspension is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low back pain; Ibuprofen Oral Suspension can also be used in soft tissue injuries such as sprains and strains.

Ibuprofen Oral Suspension is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for symptomatic relief of headache; including migraine headache.

Ibuprofen Oral Suspension is indicated in short-term use for the treatment of pyrexia in children over one year of age.

4.2 Posology and method of administration
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

For oral administration, preferably with or after food.

Adults: the recommended dosage of Ibuprofen Oral Suspension is 1200-1800 mg daily in three to four divided doses. Some patients can be maintained on 600-1200 mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400 mg in divided doses.

Children: Not recommended for children weighing less than 7 kg. For fever and pain, the daily dosage of Ibuprofen Oral Suspension is 20 mg/kg of bodyweight in divided doses. This can be achieved as follows:

Children 1-2 years: One 2.5 ml spoonful (50 mg) to be taken three to four times in 24 hours.
Children 3-7 years: One 5 ml spoonful (100 mg) to be taken three to four times in 24 hours.
Children 8-12 years: Two 5 ml spoonfuls (200 mg) three to four times in 24 hours.

For juvenile rheumatoid arthritis the usual daily dosage is 30-40 mg/kg/day in three to four divided doses.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If Ibuprofen Oral Suspension is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. If renal or hepatic function is impaired the dosage should be assessed individually.

4.3 Contraindications

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

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

Ibuprofen Oral Suspension is contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).

Severe heart failure, renal failure and hepatic failure (see section 4.4).

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

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

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 section 4.2, and GI and cardiovascular risks below).

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

Elderly:
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 disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8)

Gastrointestinal bleeding, ulceration and perforation:
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).
Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

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

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

The elderly are at increased risk of the serious consequences of adverse reactions.

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

**Cardiovascular and cerebrovascular effects:**
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

**SLE and mixed connective tissue disease:**
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

**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 higher risk for these reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

**Impaired female fertility:**
There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment. In women attempting to conceive or who are undergoing investigation of infertility, withdrawal of Ibuprofen should be considered.

**Excipients of Ibuprofen 100 mg/5ml Oral suspension**
Due to the presence of liquid maltitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217) may cause allergic reactions (possibly delayed).

This medicinal product contains 0.48 mmol of sodium per 5 ml of suspension. This should be taken into consideration for patients on a controlled sodium diet.
4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Antihypertensives: reduced antihypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity with NSAIDs.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

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

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in last trimester of pregnancy is contraindicated.

The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

In the limited studies so far available, NSAIDs can appears in the breast milk in very low concentrations, NSAIDs should, if possible, be avoided when breast-feeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.
4.7 Effects on ability to drive and use machines
Dizziness, drowsiness, visual disturbances, fatigue or headaches are possible undesirable effects after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects
Gastrointestinal: the most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis and ulcerative stomatitis, exacerbation of colitis and Crohn’s disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis and duodenal ulcer have been observed. Pancreatitis has been reported very rarely.

Hypersensitivity: hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular: Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Other adverse reactions reported less commonly include:
- Renal: nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.
- Hepatic: abnormal liver function, hepatitis and jaundice.
- Neurological & special senses: visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.
- Haematological: thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.
- Dermatological: Bullous reactions including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity (see 'hypersensitivity' for other skin reactions).

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

a) Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, dizziness, excitation and disorientation, fainting 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.

b) Therapeutic measure
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.

Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient’s clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: MO1A E01.

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic product, non steroid, propionic acid derivative.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug’s therapeutic effects as an NSAID are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

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

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed from the gastrointestinal tract. Peak serum concentrations occur 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed 1-2 hours after administration. The elimination half-life is approximately 2 hours. Ibuprofen is metabolised in the liver to two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
Xanthan gum
Carboxy/methylcellulose sodium
Microcrystalline cellulose
Liquid maltitol (E965)
Citric acid monohydrate
Sodium citrate
Sodium benzoate
6.2 **Incompatibilities**
Not to be mixed with other medicinal products.

6.3 **Shelf life**
24 months.

6.4 **Special precautions for storage**
Do not store above 25°C.
Keep container in the outer carton and protect from light.

6.5 **Nature and contents of container**
An amber-coloured polyethylene terephthalate (PET) bottle containing 500 ml Ibuprofen Oral Suspension sealed with a polypropylene, tamper-evident child resistant cap fitted with a low density polyethylene liner.

6.6 **Special precautions for disposal**
Shake well before use.

7 **MARKETING AUTHORITY HOLDER**
STD Chemicals Ltd,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 **MARKETING AUTHORIZATION NUMBER(S)**
PL 36390/0042

9 **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
02/09/2011

10 **DATE OF REVISION OF THE TEXT**
02/09/2011
IBUPROFEN 100 MG/5 ML ORAL SUSPENSION
PL 36390/0042

PATIENT INFORMATION LEAFLET

1. WHAT IBUPROFEN SUSPENSION IS AND WHAT IT IS USED FOR

Ibuprofen oral suspension contains 100 mg of the active ingredient ibuprofen in 5 ml.

Ibuprofen belongs to a group of drugs called non-steroidal anti-inflammatory drugs (also known as NSAIDs), which relieve pain and reduce inflammation. Ibuprofen suspension is used to treat conditions affecting the joints and muscles such as swollen joints, frozen shoulder, low back pain, rheumatoid arthritis (inflammation of the joints and tendons), osteoarthritis (inflammation of the joints), osteoporosis, and other conditions of the muscles, bones, and tendons.

Ibuprofen suspension can also be used:
- in soft tissue injuries such as sprains and strains
- to relieve mild to moderate pain in dysmenorrhea (menstrual pain), dental pain, and pain after an operation
- to relieve mild to moderate pain due to headache, including migraine headaches
- Ibuprofen suspension can be used for the short-term treatment of pyrexia (fever) in children over one year of age.

2. BEFORE YOU TAKE IBUPROFEN SUSPENSION

Do not take Ibuprofen Suspension if you:
- are allergic (hypersensitive) to ibuprofen or any of the other ingredients in ibuprofen suspension (see list of ingredients in Section 6). An allergic reaction may include skin rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue
- have had attacks of asthma, or an allergic reaction such as urticaria (hives) or angioedema (swelling of the face and throat) or rhinitis (inflammation of the lining of the nose) when you have taken aspirin, ibuprofen or any other NSAID (non-steroidal anti-inflammatory drugs)
- suffer from or have previously had stomach ulcers or stomach bleeding
- have suffered chronic indigestion
- have had severe heart failure, kidney failure or liver failure
- are in your last trimester of pregnancy.

Take special care with ibuprofen suspension and talk to your doctor if you:
- are taking any other painkillers, NSAIDs or aspirin
- are taking antidepressants, SSRIs (medicines used to treat depression, anxiety, or personality disorders) suffer from systemic lupus erythematosus or mixed connective tissue disease (a condition which causes pain, swelling, and fever)
- suffer from epilepsy or have ever had seizures
- have had a history of ulcers or acid reflux - you should report any digestive symptoms, especially if you are elderly, particularly blood in your stools or vomit. If you develop an ulcer or have bleeding, you should stop treatment.
- have had hypertension (high blood pressure) or heart failure
- have heart disease, peripheral arterial disease (a disease of the blood vessels), or cerebrovascular disease (a disease of the blood vessels in the brain)
- are at risk of heart disease because you have high blood pressure, high lipid levels, diabetes, or you smoke
- are trying to become pregnant
- have a kidney, heart or liver disorder.

Please note:
If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and seek immediate medical help:
- Pain in your face or jaws
- Pass black tarry stools
- Vomits any blood or dark particles that look like coffee grounds

STOP TAKING the medicine and call your doctor if you experience:
- Indigestion or heartburn
- Abdominal pain (pain in your stomach) or other abnormal stomach symptoms.
Ibuprofen suspension may be associated with a small increased risk of heart attack (myocardial infarction) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

If you develop any skin reaction you should stop taking this medicine and contact your doctor immediately (see sections 4 Possible side effects).

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. This is particularly true of the following as they may interact with your ibuprofen suspension.
- other painkillers (including capsaicin)
- corticosteroids (drugs that reduce inflammation such as hydrocortisone)
- anticoagulants (blood thinners)
- oral contraceptives (treatments for heart failure such as digoxin)
- lithium (treatment for mental illness)
- methotrexate (used for rheumatoid arthritis and cancer)
- diuretics (water tablets)
- antihypertensives (drugs that reduce blood pressure)
- rifampicin (a drug used for tuberculosis)
- benzodiazepines (a type of antiepileptic agent)
- clopidogrel and ticagrelor (a treatment to prevent re-occlusion after a transplant)
- anticoagulant/painkillers (used for coronary problems and to prevent blood clots)
- SSRIs (selective serotonin reuptake inhibitors — antidepressants for anxiety and personality disorders)
- dopamine (anti-convulsant treatment for CVH)
- medicines that are anti-epileptics (e.g. those that prevent epilepsy)
- some medicines that reduce high blood pressure (ACE inhibitors such as captopril, beta-blockers, such as atenolol, or angiotensin II receptor antagonists such as losartan), and other medicines may affect or be affected by treatment with ibuprofen. You should therefore always ask the advice of your doctor or pharmacist before you take ibuprofen with other medicines.

It may still be all right for you to be given ibuprofen suspension and your doctor will be able to decide what is suitable for you.

Taking ibuprofen suspension with food and drink
Ibuprofen suspension should be taken by mouth, preferably with or after food.

Pregnancy and breastfeeding
Do not take ibuprofen oral suspension during the last trimester of pregnancy. You should not take ibuprofen suspension while pregnant or breastfeeding unless your doctor has advised you to do so. Ask your doctor or pharmacist for advice before taking any medicine.

Ibuprofen suspension may make it more difficult for you to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

Driving and using machines
Ibuprofen may cause dizziness, sleepiness, visual disturbances or headaches. If you have any of these symptoms, do not drive or operate machinery.

Important information about some of the ingredients of Ibuprofen Suspension
- Sodium (sodium chloride (E250) and sodium propyl (E217)) parabens and sorbates may cause allergic reactions which could possibly be delayed.
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- This medicine contains 0.48 mmol of sodium per 5 mL. To be taken into consideration by patients on a controlled sodium diet.

3. HOW YOU TAKE IBUPROFEN SUSPENSION

Dosage
Always take ibuprofen suspension exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Take with or after food.

Adults
- The usual dose for adults is 1200 mg to 1200 mg daily in 3 or 4 divided doses. The maximum dose is 3000 mg per day.

Children
- Not recommended for children weighing less than 7 kg.
- The usual dose for children with fever or pain is 20 mg/kg of body weight in divided doses. (300 mg to 300 mg maximum dose is 3.6 mg/kg in divided doses. (2.6 mg/kg maximum dose is 60 mg/kg in divided doses.
- Children 3-7 years: One 5 ml spoonful (75 mg) to be taken three to four times in 24 hours.
- Children 8-12 years: Two 5 ml spoonfuls (150 mg) a day in divided doses in 24 hours.
- For fever, paracetamol should be used as usual dose is 30-40 mg/kg in divided doses. In fever, ibuprofen suspension is being used to treat fever it should not be used long term and should not be given to children under one year of age.

Excessive
- The elderly are more susceptible to side effects from ibuprofen so the lowest effective dose should be taken.
- Elderly patients should be monitored regularly during the treatment to check that there is no bleeding in the stomach or gut.

If you take more ibuprofen suspension than you should
If you, or a child you are giving this medicine to, have accidentally taken more than the stated dose, you must contact your doctor or local casualty department as soon as possible. Symptoms of an overdose include nausea (feeling sick), vomiting (being sick), stomach pain, stomach bleeding, diarrhoea, headaches, dizziness, feeling excited, delirium, fainting, fits and coma. If you are unconscious your condition may get worse.

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If you forget to take ibuprofen suspension
If you have forgotten to take your medicine, take it as soon as you remember unless it is almost time for your next dose. Do not take a double dose to make up for the one you missed.

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

4. POSSIBLE SIDE EFFECTS

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

All medicines can cause side effects, although serious side effects are very rare. Stop taking ibuprofen and tell your doctor straight away if you get any sudden weakness, difficulty in breathing, swelling of the eyelids, face or lips, skin peeling, skin rash or itching (especially affecting your whole body).

The following side effects have been reported:

Haematological: feeling sick, vomiting, diarrhoea, decreased appetite, pain on injection, abnormal liver function tests, inflammation of the digestive tract, mouth ulcers, rash, tightness in the chest, pain or pressure in the throat and accelerated heartbeat.

Neurological: headache, dizziness, flushing, feeling faint, feeling sick, fits, convulsions, unconsciousness, breathing difficulties, fits or convulsions.

Skin and eyes: sudden or severe allergic reaction (angio-oedema or urticaria) or rash.

If you have systemic lupus erythematosus (your doctor would have told you if you have this), you may get side effects such as a stiff neck, headaches, nausea (feeling sick), vomiting (being sick), fever or diarrhoea.

Less common side effects:

- General skin conditions including peeling, blistering, red spots, and swelling, and sensitivity to light.
- Ibuprofen can sometimes cause kidney damage, decreased liver function, fever, inflammation, and jaundice (yellow skin and eyes).
- Abnormal chest pain, heart attack, pain and tenderness, depression, constipation, hallucinations (seeing or hearing things that are not there), ringing in the ears, vertigo (spinning sensation), dizziness, weakness, tiredness, epilepsies and generally feeling unwell.

If you have systemic lupus erythematosus (your doctor would have told you if you have this), you may get side effects such as a stiff neck, headaches, nausea (feeling sick), vomiting (being sick), fever or diarrhoea.

Blood disorders include reduction in red and white blood cells and blood platelets.

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

If you have any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IBUPROFEN SUSPENSION

Ibuprofen suspension should be kept out of the reach and sight of children.

Do not store above 25°C.

Keep container in the outer carton and protect from light.

Do not take this medicine after the expiry date shown on the label.

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

6. FURTHER INFORMATION

What ibuprofen suspension contains:

The active substance is ibuprofen.

The other ingredients are: sodium hydroxypropylcellulose (E467), sodium propylparaben, sorbic acid, benzoic acid, sodium citrate, sodium benzoate, potassium sorbate, sodium polycarbophil, Natural Orange Flavour, Orangetaste No 1 Flavour (which contains propylene glycol), and purified water.

What ibuprofen suspension looks like and contents of the pack:

Ibuprofen suspension is a white-coloured, orange flavoured suspension.

An amber-coloured plastic bottle containing 500 ml ibuprofen suspension sealed with a child resistant cap.

Marketing Authorisation Holder and Manufacturer:

The Product Licence holder is Sandoz Limited, Willans House, Willans Road, Water Newton, Cambridge, CB3 9XW.

The manufacturer responsible for batch release is Nicedot Ltd, 57 High Street, Oxted, Surrey, RH8 9LF.

This leaflet was last revised in August 2011.
IBUPROFEN 100 MG/5 ML ORAL SUSPENSION
PL 36390/0042

LABELLING

BOTTLE CARTON

IBUPROFEN 100 MG/5 ML ORAL SUSPENSION
PL 36390/0042

LABELLING

BOTTLE LABEL

For oral use.
Use as directed by a doctor. Shake well.
Please read the information leaflet before taking this medicine.
Each 5 ml contains 100 mg Ibuprofen Ph. Eur.
Also contains: liquid maltitol, E217, E219 and 0.48 mmol/5ml of sodium.
See leaflet for further information.
Keep container in the outer carton to protect from light.
Do not store above 25°C.
Keep all medicines out of reach and sight of children.

Distributor:
NeoLab Ltd, 57 High Street,
Odham, Hants, RG29 1LF.
PL 36390/0042
PL Holder
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