The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in April 2015.

1. Name of the medicinal product

NUROFEN® LIQUID CAPSULES 200mg
NUROFEN® TABLETS 200mg

2. Qualitative and Quantitative composition

Active Ingredient
Ibuprofen 200 mg
For excipients, see 6.1.

3. Pharmaceutical form

Nurofen Liquid Capsules 200mg
0.6 ml oval capsule with a translucent red gelatin shell, containing a clear liquid with an identifying motif in white.
Nurofen Tablets 200mg
Coated Tablet.
A white to off-white, biconvex, round, sugar coated tablet printed 'Nurofen' in black on one face.

4. Clinical particulars

4.1 Therapeutic indications

Nurofen Tablets 200mg / Nurofen Liquid Capsules 200mg
Adults and children over 12 years:
Relief of mild to moderate pain such as headache, toothache, menstrual pain, backache, muscular pain, anti-inflammatory for rheumatic diseases, reduction of fever.

4.2. Posology and method of administration

For oral administration and short-term use only.

During short-term use, if symptoms persist or worsen the patient should be advised to consult a doctor.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.

If in children and adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.
If in adults the product is required for more than 10 days, or if the symptoms worsen the patient should consult a doctor.

The tablets/Liquid Capsules should not to be used for more than 10 days for the treatment of pain, or for more than 3 days for the treatment of fever, unless instructed by the physician.

Nurofen Tablets 200 mg / Nurofen Liquid Capsules 200 mg
Adults and Children 12 Years of Age and Over
1-2 tablets/liquid capsules up to three times a day as required.
Leave at least four hours between doses.
Do not take more than 6 tablets/liquid capsules in any 24 hour period.
Not for use by children under 12 years of age.

4.3. Contraindications

Patients with known hypersensitivity to ibuprofen or any other constituent of the medicinal product.

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

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

Patients with a history of, or existing peptic ulceration gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see section "special warnings and precautions for use").

Patients with severe hepatic failure, severe renal failure or severe heart failure (see also section "special warnings and precautions for use").

During the last trimester of pregnancy as there is a risk of premature closure of the fetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labor may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section "pregnancy and lactation").

4.4. Special warnings and precautions for use
Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Use with concomitant NSAIDs, including cyclo-oxygenase-2 specific inhibitors – increased risk of adverse reactions (see section "Interaction with other medicinal products and other forms of interaction).

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

Other NSAIDs:
The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section "Interaction with other medicinal products and other forms of interaction).

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

Renal:
Renal impairment as renal function may further deteriorate (see sections "contraindications" and "undesirable effects").

Hepatic:
Hepatic dysfunction (see Sections "contraindications" and "undesirable effects")

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g.≤ 1200mg daily) is associated in an increased risk of myocardial infarction.

Impaired female fertility:
There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis

may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Gastrointestinal:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section "undesirable effects").
GI bleeding, ulceration or perforation, which can be fatal has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of GI events.

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

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section "Interaction with other medicinal products and other forms of interaction).

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

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

Advice for patients with sugar-related disorders:

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.
If symptoms persist or worsen, or if new symptoms occur, consult your doctor or pharmacist.

Use in Pediatrics
Nurofen Tablets/Liquid Capsules and Nurofen Forte Tablets are not to be used in children under 12 years of age.

***Nurofen Tablets* 200 mg**:
Advice for patients on a controlled sodium diet:
This medicinal product contains 1.1 mmol (or 25.3 mg) of sodium per 2 doses (2 tablets). To be taken into consideration by patients on a controlled sodium diet.

4.5. Interactions with other medicinal products and other forms of interaction
Ibuprofen (like other NSAIDs) should be avoided in combination with:

• ***Aspirin***: unless low-dose aspirin (not above 75mg daily) has been advised by a doctor as this may increase the risk of adverse reactions (see section "special warnings and precautions for use").
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 "pharmacodynamics properties").

• ***Other NSAIDs including cyclooxygenase-2 selective inhibitors***: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section "special warnings and precautions for use").

Ibuprofen should be used with caution in combination with:

• ***Corticosteroids****:* as these may increase the risk of gastrointestinal ulceration or bleeding (see section "special warnings and precautions for use").
• ***Antihypertensives and diuretics****:* since NSAIDs may diminish the effects of these drugs. . In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
• ***Anticoagulants****.* NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section "special warnings and precautions for use").
• *Anti-**platelet agents and selective serotonin reuptake inhibitors (SSRIs)**:* increased risk of gastrointestinal bleeding (see section "special warnings and precautions for use").
• ***Cardiac glycosides****:* NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
• ***Lithium****.* There is evidence for potential increase in plasma levels of lithium.
• ***Methotrexate****:* There is evidence for the potential increase in plasma levels of methotrexate.
•***Ciclosporin****:* Increased risk of nephrotoxicity.
• ***Mifepristone****:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
• ***Tacrolimus****:* Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
• ***Zidovudine****:* Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
• ***Quinolone antibiotics****: Animal* data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

4.6. Pregnancy and lactation:
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 gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryfoetal 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 should not be given unless clearly necessary. If Nurofen 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 oligohydroamniosis;
the mother and the neonate, at the end of the 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 is contraindicated during the third trimester of pregnancy.

Lactation/Breastfeeding:
In limited studies, ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breastfed infant adversely.

See section "special warnings and precautions for use" regarding female fertility.

4.7. Effects on ability to drive and use machines
None expected at recommended dose and duration of therapy.

4.8. Undesirable effects

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

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

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

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

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

Gastrointestinal disorders
Uncommon: abdominal pain, dyspepsia and nausea.

Rare: diarrhea, flatulence, constipation and vomiting.

Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.

Not Known : Exacerbation of ulcerative colitis and Crohn's disease (see section "special warnings and precautions for use").

Nervous System
Uncommon:
Very rare: Aseptic meningitis

Renal and Urinary Disorders
Very rare: Decrease of urea excretion and oedema can occur., acute renal failure. Papillary necrosis, especially in long-term use, associated with increased serum urea and oedema

Not Known : Renal insufficiency

Liver/Hepatobiliary Disorders
Very rare: Liver disorders

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

Skin and Subcutaneous Tissue Disorders
Uncommon: Various skin rashes.
Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.-

Immune system disorder:
Hypersensitivity reactions consisting of[1]:
Uncommon : Urticaria and pruritus

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

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

Not Known: Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.

Hypersensitivity Reactions:
Exacerbation of asthma and bronchospasm.

Cardiac disorder:
Not Known : Cardiac failure and oedema

Vascular Disorder
Not Known : Hypertension

Investigations
Very rare : Decreased haemoglobin levels

Description of Selected Adverse Reactions

[1] Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, 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).

[2]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or

disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

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

Symptoms:
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma loss of consciousness. 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. Pharmacodynamic properties
ATC Code: M01A E01 Propionic acid derivative.
Ibuprofen is a propionic acid derivative 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.

Clinical evidence demonstrates that when 400mg of ibuprofen is taken the pain relieving effects can last for up to 8 hours.

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 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no relevant effect is considered to be likely for occasional ibuprofen use.

5.2. Pharmacokinetic properties
Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins.

Nurofen Liquid capsules 200mg consist of ibuprofen 200 mg dissolved in a hydrophilic solvent inside a gelatin shell. On ingestion, the gelatin shell disintegrates in the gastric juice releasing the solubilised ibuprofen immediately for absorption. The median peak plasma concentration is achieved approximately 30 minutes after administration.
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

Nurofen Tablets 200mg Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.
Elimination half-life is approximately 2 hours.

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

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

5.3. Preclinical safety data
No relevant information, additional to that contained elsewhere in the SPC.

6. Pharmaceutical particulars
6.1. List of excipients
Nurofen Liquid Capsules 200 mg:
Polyethylene glycol 600, Gelatine, Povidone K17, Vitamin E, Maltitol liquid, Sorbitol liquid, Purified water, Ponceau 4R, Opacode MS-78-18011 or Opacode S-1-7020, Titanium dioxide, Shellac dewaxed.

Nurofen Tablets 200 mg:
Sucrose*, Sodium citrate, Talc, Croscarmellose sodium, Stearic acid, Titanium dioxide, Colloidal anhydrous silica, Carmellose sodium, Acacia spray dried, Sodium laurilsulfate, , Macrogol 6000, Opacode monogramming ink-S-1-277001 Black
** Sugar content: 116.1 mg/tablet.*

6.1. Shelf life
Nurofen tablets 200 mg, -36 months
Nurofen liquid capsules 200 mg - 24 months

6.2. Special precations for storage
Store below 25^0C

6.3. Presentation
Nurofen Tablets 200 mg : 12, 24, 48 tablets.
Nurofen Liquid Capsules 200 mg : 4, 10, 16, 20 and 40 Liquid Capsules.

7. Manufacturer
Reckitt Benckiser Healthcare Ltd.,
Nottingham, England

8. Registration holder
Reckitt Benckiser (Near east) Ltd.,Hod Hasharon 45240

9. Registration number
NUROFEN® LIQUID CAPSULES 200mg :127 55 30584 00
NUROFEN® TABLETS 200mg :132 32 31025 00