IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0979/032/004
Case No: 2057368

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Reckitt Benckiser Ireland Ltd

7 Riverwalk, **Citywest Business Campus**, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Nurofen 200 mg Meltlets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/04/2009** until **13/05/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen 200 mg Meltlets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 200 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.
White to off-white round tablet with characteristic lemon odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an anti-inflammatory, analgesic and antipyretic for short term management of mild to moderate pain such as is associated with headache, dental pain, feverishness, period pain, muscular strain, backache and for the management of the symptoms of head colds and influenza.

4.2 Posology and method of administration

For oral administration.
Place a tablet on the tongue, allow it to dissolve and then swallow; no water is required.
Adults and children over 12 years: Initial dose is 400 mg and subsequently if necessary, 200 mg to 400 mg every four hours with a maximum of 1200 mg in any 24 hour period.
Not for use by children under 12 years of age.
Elderly: no special dosage modifications are required.

4.3 Contraindications

Severe heart failure.

Hypersensitivity to any of the constituents, aspirin, or other NSAIDs.

History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding or other gastrointestinal disorder.
Patients with a history of bronchospasm, asthma, rhinitis, or urticaria associated with aspirin or other non-steroidal anti-inflammatory drugs.
Use in children under 12 years of age.

You should not take Nurofen Meltlets if you have phenylketonuria or are intolerant to phenylalanine, each tablet contains aspartane equivalent to 8.4 mg phenylalanine.

4.4 Special warnings and precautions for use

The use of Nurofen 200 mg Meltlets with concomitant NSAIDs including cycloosygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2 Posology and method of administration, and GI and cardiovascular risks below).

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, Posology and methos of administration).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without any warning symptoms or a pervious history of serious 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 4.3, Contraindications), 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 4.5, Interaction with other medicinal products and other forms of interaction).

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 or anti-platelet agents such as aspirin (see Section 4.5, Interaction with other medicinal products and other forms of interaction).

When GI bleeding or ulceration occurs in patients receiving Nurofen 200 mg Meltlets, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's Disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).

Caution is required in patients with cardiac or hepatic impairment. Similarly caution is required in patients with renal impairment since renal function may deteriorate. The dose should be as low as possible and renal function monitored.

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 and oedema have been reported in association with NSAID therapy.

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

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

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

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, Undesirable effects). 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 200 mg Meltlets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.

Asthma sufferers, anyone allergic to or taking any other painkiller or receiving regular treatment or pregnant women should only take Nurofen Meltlets after consulting their doctor.
If symptoms persist for more than 3 days, worsen or new symptoms develop, patients should be advised to consult their doctor.

4.5 Interaction with other medicinal products and other forms of interaction

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4, Special warnings and precautions for use).
Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4, Special warnings and precautions for use).
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4, Special warnings and precautions for use).

Care should be taken in patients treated with any of the following drugs as interactions have been reported:
Anti-hypertensives: reduced anti-hypertensive effect.
Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels.
Lithium: decreased elimination of lithium.
Methotrexate: decreased elimination of methotrexate.
Cyclosporon: increased risk of nephrotoxicity with NSAIDs.
Other NSAIDs: concomitant use of two or more NSAIDs.
Corticosteroids: increased risk of gastrointestinal bleeding.
Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
Probenecid: reduction in metabolism and elimination of NSAID and metabolites.
Oral hypoglycaemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.
Anticoagulants: there is limited evidence of enhancement of oral anticoagulants.

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).

4.6 Pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animals, the use of Nurofen Meltlets during pregnancy should, if possible, be avoided.
The onset of labour may be delayed and the duration of labour increased.
In limited studies, ibuprofen appears in the breast milk in very low concentrations and is unlikely to affect the breast-fed infant adversely.

4.7 Effects on ability to drive and use machines

None.

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, Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4, Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Cardiovascular: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Cardiovascular and cerebrovascular effects: 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 or arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4, Special warnings and precautions for use).

Skin: Pruritis, urticaria. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen. Cullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).
Renal: Papillary necrosis which can lead to renal failure.
Others: Hepatic dysfunction, headache, dizziness, hearing disturbance. Rarely, thrombocytopenia.

4.9 Overdose

Symptoms include nausea, vomiting, dizziness, hypotension and, rarely, loss of consciousness. Large overdoses are generally well tolerated when no other drugs are involved. No specific antidote is available and supportive therapy is indicated. Treatment consists of gastric lavage and if necessary correction of serum electrolytes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties

Ibuprofen is a propionic acid derivative, having analgesic, anti-pyretic and anti-inflammatory activity. The drug's therapeutic effects as a non-steroidal anti-inflammatory drug are thought to result from inhibitory activity on prostaglandin synthetase.

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 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 clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Nurofen Meltlets consist of taste masked ibuprofen granules incorporated into a compressed tablet. When the tablet is placed on the tongue it rapidly dissolves to release the ibuprofen granules. The ibuprofen granules can then be swallowed without the need for water.
When Nurofen Meltlets reach the stomach the ibuprofen granules rapidly dissolve in the gastric juices releasing mainly unionized ibuprofen acid, which is the only entity absorbed into the plasma.
Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins and diffuses into the synovial fluid.

Peak plasma concentrations from Nurofen Meltlets occur approximately 1-2 hours after administration. When taken with food, peak plasma levels may be delayed.
Ibuprofen is metabolised in the liver to two major inactive metabolites and the kidney excretes these together with unchanged ibuprofen either as such or as major conjugates. Excretion by the kidney is both rapid and complete. Elimination half life is approximately 2 hours.
No significant difference in pharmacokinetic profile is observed in the elderly.

5.3 Preclinical safety data

There is no preclinical safety data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylcellulose
Silicon dioxide
Hypromellose
Mannitol
Aspartame
Croscarmellose sodium
Magnesium stearate
Flavour (lemon flavours, maltodextrin).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The orodispersible tablets are packed in a cold formed blister pack. The blister pockets are formed from 60 µm PVC/ 45 µm aluminium/ 23 µm polyamide film heat sealed to 20 µm aluminium foil blister lid.

The blister trays are packed into cardboard cartons containing 4 and 12 orodispersible tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Ltd
7 Riverwalk,
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0979/032/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristaion: 14 May 2004

10 DATE OF REVISION OF THE TEXT

April 2009