Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Advance 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ibuprofen 200mg (as lysine salt).
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, film-coated capsule shaped tablet, printed with an identifying logo in black on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an anti-inflammatory, analgesic and anti-pyretic for the relief of mild to moderate pain, such as headache, migraine, dental pain, feverishness, period pain, muscular strain and backache. For the symptomatic relief of fever, colds and influenza.

4.2 Posology and method of administration

Posology
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

If this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Adults and children over 12 years: Initial dose is one or two tablets and subsequently if necessary, one or two tablets every four hours with a maximum of 6 tablets in a 24 hour period i.e. a maximum dose of 1200mg in a 24 hour period. For short-term use only (see above).

Children under 12 years of age: Not recommended.
Elderly: See section 4.4 Special Warnings and Precautions for Use.

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed please refer to section 4.4. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

4.3 Contraindications

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 known history of hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to ibuprofen (the active substance) or any of the excipients, acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

Use in children under 12 years of age.

Patients with severe hepatic failure or severe renal failure (See Section 4.4).

Severe heart failure (NYHA Class IV).

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

During the last trimester of pregnancy (See Section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration to relieve symptoms. Where prolonged therapy is required, patients should be reviewed regularly.
Patients allergic to or taking any other pain reliever, receiving regular medical treatment, the elderly and pregnant women should only take Nurofen Advance Tablets after consulting their doctor. If symptoms persist for more than 3 days or worsen or if new symptoms occur, stop treatment at once and consult your doctor.
Other NSAIDs: The use of Nurofen Advance 200mg Tablets 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). Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.
Gastrointestinal effects: 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 previous 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), 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).
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 antiplatelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving Nurofen Advance 200mg Tablets, 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).
Respiratory: Bronchospasm may be precipitated in patients suffering from, or with a previous history of, bronchial asthma or allergic disease.
SLE and mixed connective tissue disease: Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).
Severe skin reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported 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. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.
Masking of symptoms of underlying infections:
Nurofen Advance 200mg Tablets can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Nurofen Advance 200mg Tablets are administered for fever or pain relieve in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.
Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. It is advisable to avoid use of ibuprofen in cases of varicella.
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.

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 and oedema have been reported in association with NSAID therapy. Caution is required in patients with cardiac or hepatic impairment.
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) 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/day) is associated with an increased risk of arterial thrombotic events. Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.
Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.
Renal: Similarly caution is required in patients with renal impairment, since renal function may deteriorate (see section 4.3 and 4.8). The dose should be as low as possible and renal function should be monitored. There is a risk of renal impairment in dehydrated children.
Hepatic: Hepatic dysfunction (see sections 4.3 and 4.8).
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:
Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended unless low-dose Acetylsalicylic Acid (Aspirin) (not above 75mg daily) has been advised by a doctor because of the potential of increased adverse effects (see section 4.4). Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effects of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional use (see section 5.1).

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

Ibuprofen should be used with caution in combination with any of the following drugs as interactions have been reported:

Anti-hypertensives (ACE inhibitors and Angiotensin II Antagonists): reduced anti-hypertensive effect.

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

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

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations may occur.

Lithium: decreased elimination of Lithium.

Methotrexate: decreased elimination of Methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

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

Probenecid: reduction in metabolism and elimination of NSAIDs and metabolites.

Oral hypoglycaemic Agents:
Inhibitions of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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

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

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 of haemarthroses and haematoma in HIV (positive) 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 Fertility, pregnancy and lactation

Pregnancy:
Inhibition of prostaglandin in 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 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.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus construction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given, unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Anti-natal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure for several days from gestational week 20 onward. Treatment should be discontinued if oligohydramnios or ductus arteriosus constriction are found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction (see above)

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, ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3).
Lactation/Breastfeeding:
In limited studies, ibuprofen and its metabolites appear in the breast milk in very low concentration (0.0008% of the maternal dose) and is unlikely to affect the breast-fed infant adversely.
Fertility:
There is some evidence that medicinal products which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see Section 4.4 regarding female fertility).

4.7 Effects on ability to drive and use machines

No adverse effects known.

4.8 Undesirable effects

Possible side effects are those experienced with ibuprofen acid (maximum 1200mg Ibuprofen per day), in short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.
Adverse events which have been associated with Ibuprofen are given below, tabulated by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and < 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.

System Organ Class	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders1
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus2
	Very rare	Swelling face, swollen tongue, pharyngeal oedema, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)2
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis3
Ear and Labyrinth Disorders	Not Known	Hearing Impaired
Cardiac Disorders	Not known	Cardiac failure andoedema4
Vascular Disorders	Not known	Hypertension4
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasmordyspnoea2
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia5
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis6. Mouth ulceration and gastritis
	Not known	Exacerbation of colitis and Crohn'sdisease7
Hepatobiliary Disorders	Very rare	Liver disorder
	Not Known	Hepatic function abnormal
Skin and Subcutaneous Tissue Disorders	Uncommon	Skinrash2
	Very rare	Bullous reactions, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis2
	Not Known	Rash maculo-papular, erythema. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary Disorders	Very rare	Acute renal failure8
Investigations	Very rare	Haemoglobin decreased
Infections and infestations	Very rare	Exacerbation of infections related inflammation (e.g. development of necrotizing fasciitis), in exceptional cases, severe skin infections and soft-tissue complication may occur during a varicella infection.

Description of Selected Adverse Reactions
[1]Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
[2]Hypersensitivity reactions: These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract

reactivity, including asthma, aggravated asthma, bronchospasm, and dyspnoea or (c) various skin reactions, including pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.
[3]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 and mixed connective tissue disease).
[4]Clinical trial and epidemiological studies 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 (e.g. myocardial infarction or stroke), (see section 4.4).
[5]The most commonly observed adverse events are gastrointestinal in nature.
[6]Sometimes fatal, particularly in the elderly.
[7]See Section 4.4.
[8] Especially in long term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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

Symptoms
For most patients who have ingested clinically important amount of NSAIDs develop no more than symptoms including nausea, vomiting, dizziness, drowsiness, hypotension, epigastric pain, or more rarely, diarrhoea or and rarely, loss of consciousness. Tinnitus, headache and gastrointestinal bleeding are also possible. Large overdoses are generally well tolerated when no other drugs are involved.
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
No specific antidote is available management should be symptomatic, supportive, including the maintenance of a clear airway, monitoring of cardiac and vital signs until stable and, if necessary, include correction of serum electrolytes. 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:** M01AE01.

Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative, having analgesic, anti-inflammatory and antipyretic activity. Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. The therapeutic effects of ibuprofen as a non-steroidal anti-inflammatory drug to reduce inflammatory pain, swellings and fever, are thought to result from inhibitory activity on prostaglandin synthetase. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Each tablet contains 342 mg of ibuprofen lysine. 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.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Most pharmacokinetic data obtained following the administration of ibuprofen acid also apply to Nurofen Advance Tablets.

Ibuprofen is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1-2 hours after administration of ibuprofen acid. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Nurofen Advance Tablets, with peak plasma concentrations occurring approximately 35 minutes after administration.

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

Following ibuprofen is metabolimin the liver (hydroxylation, carboxylation and conjugation) to two inactive metabolites these, together with unchanged ibuprofen, are excreted mainly by the kidney either as such or as conjugates (90%), but also with the bile. Excretion by the kidney is both rapid and complete.

The elimination half-life of ibuprofen acid is approximately 2 hours.

The drug is extensively bound to plasma proteins. Plasma-protein binding is about 99%. Ibuprofen diffuses into the synovial fluid.

Product specific pharmacokinetic properties:
The time to reach plasma concentration (Tmax) is greatly reduced for the ibuprofen lysine product compared with the equivalent ibuprofen acid product.
A pharmacokinetic study has reported a Tmax of 35 minutes for the ibuprofen lysine 342 mg product in the fasted state, compared with a time of 80 minutes for the equivalent strength ibuprofen acid product.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Sodium starch glycolate
Magnesium stearate
Hypromellose
Talc
Opaspray White M-1-7111B (contains hypromellose and titanium dioxide (E171))
Opacode Black S-1-8152HV (Contains iron oxide (E172))
Shellac
Soya lecithin
Antifoam DC 1510 (contains polydimethylsiloxane)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

A blister pack consisting of opaque, white 250µm polyvinyl chloride (PVC)/23µm polychlorotrifluoroethylene (Aclar) laminate heat sealed to 20µm aluminium foil.

Or

A blister pack consisting of opaque, white 250µm polyvinyl chloride (PVC)/40 gsm polyvinylidene chloride (PVdC) laminate heat sealed to 20µm aluminium foil.

The blisters are packed in cardboard cartons.

Pack sizes: 2, 4, 6, 10, 12, 20, 24, 28, 32, 36, 40 and 48 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0979/075/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13th July 2006.

10 DATE OF REVISION OF THE TEXT

May 2023