Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Plus Tablets
Ibuprofen 200mg
Codeine Phosphate Hemihydrate 12.8 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Ibuprofen 200mg and Codeine Phosphate Hemihydrate 12.8mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

Product imported from UK:
Nurofen Plus is a white film-coated, biconvex capsule-shaped tablet embossed with the logo 'N+' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of pain in such conditions as: rheumatic and muscular pain, backache, migraine, dental pain, dysmenorrhoea, feverishness, symptoms of cold and flu.

4.2 Posology and method of administration

Adults and children over 12 years:

Initially two tablets, then if necessary one or two tablets every four to six hours.

Children under 12 years:

Not suitable.

Elderly:

No special dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case dosage should be assessed individually. NSAIDs should not be used continuously over prolonged periods in the elderly for the management of arthroses without careful supervision.

Do not take more than 6 tablets in 24 hours.

4.3 Contraindications

Severe liver, kidney or heart failure.

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).

Respiratory depression, hypersensitivity (e.g. bronchospasm, asthma, rhinitis, urticaria) to Ibuprofen or Codeine or any of the excipients of this product, a history of, or existing, peptic ulceration or chronic constipation.

During the last trimester of pregnancy.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor.

4.4 Special warnings and precautions for use

The use of Nurofen Plus with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2, 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).

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 anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Nurofen Plus, 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).

Nurofen Plus tablets should be used with caution in patients with gastrointestinal disease. In patients receiving anti-coagulant therapy, prothrombin time should be monitored daily for the first few days of combined treatment.

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.

Nurofen Plus tablets should be used with caution in those with hypotension, hypothyroidism, hepatic and/or renal impairment, lupus erythematoses, mixed connective tissue disease, hypertension and/ or cardiac impairment.

The tablets should be used with caution in patients with raised intracranial pressure or head injury. Bronchospasm may be precipitated in patients suffering from or with a history of bronchial asthma or allergic disease. The possibility of cross-sensitivity with aspirin and other non-steroidal anti-inflammatory agents should be considered. If symptoms persist, consult your doctor.

Codeine is a narcotic analgesic. No more than the stated dose of this medicine should be taken. Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. It is important to consult a doctor if a patient experiences the need to use this product all the time.

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 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Nurofen Plus should be discontinued at the first appearanceof 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.

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimated indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General symptoms of opiod toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates indicate that up to 1 to 2% of the Caucasian may be ultra-rapid metabolisers.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should not be used in combination with:

Aspirin or other NSAIDs: these may increase the risk of adverse reactions in the gastrointestinal tract.
Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Anti-hypertensives and diuretics: since NSAIDs may diminish the effect of these drugs.
Anti-coagulants: 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).
Lithium: there is evidence for potential increase in plasma levels of lithium.
Methotrexate: there is evidence for potential increase in plasma levels of methotrexate.
Zidovudine: there is evidence of an increased risk of haemathroses and haematoma in HIV(+) haemophiles receiving concurrent treatment with zidovudine and ibuprofen.

Caution should be exercised in patients taking mono-amine oxidase inhibitors or thiazide diuretics or oral anticoagulants.

If you are elderly or particularly if you are receiving regular treatment from your doctor, consult your doctor before taking this medicine.

Codeine Interacts with:

Monoamine oxidase inhibitors: CNS depression or excitation may occur if codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them.

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 Fertility, pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of Ibuprofen during pregnancy should, if possible, be avoided. Ibuprofen is contraindicated in the last trimester of pregnancy as the onset of labour may be delayed and duration of labour increased.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and are unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites may be present in breast milk on very rare occasions may result in symptoms of opioid toxicity in the infant.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

Patient may become dizzy and sedated with Nurofen Plus Tablets. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The list of the following adverse effects relates to those experienced with ibuprofen in the treatment of mild to moderate pain and fever. In the treatment of other indications or under long-term treatment, additional adverse effects may occur.

Gastro-intestinal Disorders	Uncommon	Abdominal pain, dyspepsia and nausea Exacerbation of colitis and Crohn’s disease, gastritis.
	Rare	Diarrhoea, flatulence, constipation and vomiting.
	Very rare	Gasro-intestinal ulcers, sometimes with bleeding and perforation can occur
Nervous System Disorders	Uncommon	Headache
Renal and Urinary Disorders	Very rare	Decrease of urea excretion and oedema can occur Also, acute reanl failure. Papillary necrosis, especially in long-term use and increased serum urea concentrations have been reported.
Hepatobiliary Disorders	Very rare	Liver disorders,, especially in long term treatments
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 sympoms, severe

		exhaustion, nose and skin-bleeding.
Cardiovascular	Very rare	Oedema, hypertension and Cardiac failure
Cardiovascular and Cerebrovascular	Very rare	Clinical trial and epidemiology 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 4.4))
Skin and Subcutaneous Disorders	Very rare	Severe forms of skin reactions such as erythema multiforme can occur. Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrosis.
Immune System Disorders	Very rare	In patients with existing auto-immune disorders (such as 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.
Hypersensitivity Reactions	Uncommon	Hypersensitivity reactions with uticaria and pruritus.
	Very rare	Severe hypersensitivity reactions. Syptoms could be: facial, tongue and larynx swelling, dysponea, tachycardia, hypotension or severe shock. Exacerbation of asthma.
Other	Very rare	Blurred vision

Side effects to codeine include:

Gastrointestinal: gastrointestinal disorders such as constipation and nausea.

Nervous system: drowsiness.

Respiratory system: respiratory depression, cough supression.

4.9 Overdose

Symptoms of overdose with ibuprofen could be expected to include the following: vomiting, dizziness and gastro-intestinal irritation or bleeding. Nausea and vomiting are prominent features of codeine overdosage. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may also occur with a large codeine overdose.

The stomach should be emptied and activated charcoal should be taken.. Symptoms should be treated on appearance and any imbalance in electrolyte levels should be considered.

If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ibuprofen is an NSAID which acts peripherally, inhibiting prostaglandin synthesis, platelet aggregation and the action of chemical mediators of pain. Codeine is a narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be due largely to its biotransformation to morphine.

The combination of a well tolerated peripheral analgesic with a centrally acting analgesic provides optimum pain relief with a lower potential for producing side effects.

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

Ibuprofen is well absorbed from the gastrointestinal tract, is extensively bound to plasma proteins and diffuses into the synovial fluid.

The elimination half-life of both ibuprofen and codeine is approximately three hours, and both drugs are given three to four times daily. The combination of the two drugs is therefore appropriate from a pharmacokinetic viewpoint; the tablet exhibits normal release characteristics for both active substances.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycollate
Pregelatinised maize starch
Hypromellose
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the blister label and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25˚C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister packs containing 12 and 24 tablets in an over-labelled outer carton.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Limited
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1447/64/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th February 2010

10 DATE OF REVISION OF THE TEXT

November 2011