Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Plus Tablets Ibuprofen 200mg Codeine Phosphate Hemihydrate 12.8mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ibuprofen 200.0 mg and Codeine Phosphate Hemihydrate 12.8 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet (Tablet)
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.
This product is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

4.2 Posology and method of administration

Posology:

Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken up to 4 times daily at intervals of not less than 6 hours. The maximum daily dose should not exceed 6 tablets in 24 hours.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

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

Adults, the elderly and children over 12 years;
Initially two tablets, then if necessary one or two tablets every 6 hours.

Paediatric population:

Children aged less than 12 years:

Ibuprofen + Codeine combination solid dose strength products should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 & 4.4).

Nurofen Plus is contraindicated in children below the age of 12 years for the symptomatic treatment of cough and/or cold (see section 4.3).

Children aged 12 years to 18 years:
Nurofen Plus is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and or cold (see section 4.4)

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.

Method of administration
For oral administration.

Treatment goals and discontinuation

Before initiating treatment with Nurofen Plus, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment in case of prescription, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

Nurofen Plus should not be used longer than necessary.

4.3 Contraindications

Hypersensitivity to the active substances or any of the excipients listed in section 6.1.

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

Severe liver or kidney failure (see section 4.4).

Severe heart failure (NYHA Class IV).

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
Chronic constipation

Last trimester of pregnancy (See section 4.6 Pregnancy and Lactation)

Concomitant treatment with Monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment (see section 4.5).

Use of codeine containing products is contraindicated in women during breastfeeding (see section 4.6).

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

In children below the age of 12 years for the symptomatic treatment of cough and or cold due to an increased risk of developing serious and life-threatening adverse reactions.

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

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 relieve symptoms.

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 effects: 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).

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.

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.

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.
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/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. ≤ 1200mg/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

The tablets should be used with caution in patients with raised intracranial pressure or head injury.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen-containing product such as Nurofen Plus. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Respiratory: 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.

Other NSAIDs: The use of Nurofen Plus with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease: There is an increased risk of aseptic meningitis in patients with Systemic lupus erythematoses and mixed connective tissue disease using the active ingredients in this product (see section 4.8).

Renal: Renal impairment as renal function may deteriorate (see section 4.3 and 4.8). There is a risk of renal impairment in dehydrated children and adolescents.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Hepatic: Hepatic dysfunction (see section 4.3 and 4.8)

Severe cutaneous adverse reactions (SCARs): Severe cutaneous adverse reactions (SCARs) including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear, ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Masking of symptoms of underlying infections:

Nurofen Plus 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 Plus 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 case 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.

Do not take concurrently with any other codeine containing compounds.

Care is advised in the administration of codeine to patients with hypotension, asthma, decreased respiratory reserve, acute respiratory depression, obstructive airways disease, prostatic hyperplasia, hypothyroidism, adrenocortical insufficiency, shock, head injuries, conditions in which intracranial pressure is raised, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, paralytic ileus, gallstones, myasthenia gravis, a history of peptic ulcer or convulsions and also in patients with a history of drug abuse and in acute alcoholism.

Hepatobiliary disorders
Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/ibuprofen has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Codeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to the respiratory depressant effects.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Nurofen Plus. Repeated use of Nurofen Plus can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Nurofen Plus may result in overdose and/or death.

Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These

have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component.

The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Nurofen Plus and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD as well as serious outcomes. If these signs occur, patients should be advised to contact their physician. Withdrawal symptoms, such as restlessness and irritability may occur once the drug is stopped.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

If you are pregnant or are being prescribed medicines, seek the advice of a doctor before taking this product (see section 4.3).

CYP2D6 metabolism: Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation, and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	**Prevalence %**
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1 to 2%

Post-operative use in children: There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function: Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Central Sleep Apnoea: Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep related hypoxemia Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Hyperalgesia: As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Keep out of the sight and reach of children.

Each tablet contains 1.26 to 1.89mg (0.05 to 0.08 mmol) of sodium per tablet, this is to say it is essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

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

The following drug-drug interactions are known to occur in association with the ibuprofen active substance in the product.

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

Acetylsalicylic acid (aspirin): unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions especially in the gastrointestinal tract (see section 4.4). Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

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 the 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 5.1)

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 4.4).

The product should be used with caution in combination with:

CYP2D6 Inhibitors: Dependence of codeine hypoalgesia on morphine formation via CYP2D6 makes this effect liable to interaction with drugs that are inhibitors of CYP2D6. Examples of potent inhibitors of CYP2D6 are quinidine, some selective serotonin reuptake inhibitors, some neuroleptics and ritornavir.

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

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: 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 cyclooxygenase-2 selective inhibitors 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. The hypotensive actions of diuretics and anti-hypertensive agents may be potentiated when used concurrently with opioid analgesics.

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

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

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

Lithium: there is evidence for potential increases in plasma levels of lithium.

Methotrexate: there is evidence for potential increases 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 of haemarthroses and haematoma in HIV(+) haemophiles 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.

The following drug-drug interactions are known to occur in association with the Codeine active substance in the product:

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 (see section 4.3).

Moclobemide: risk of hypertensive crisis.

Hydroxyzine: Concurrent use of hydroxyzine (anxiolytics) with codeine may result in increased analgesia as well as increased CNS depressant, sedative and hypotensive effects.

Central Nervous System Depressants: The depressant effects of codeine are enhanced by depressants of the central nervous system such as other opioids, alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants or antipsychotics and phenothiazines.

The concomitant use of Nurofen Plus with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Abiraterone: Abiraterone might reduce analgesic effect of codeine by CYP2D6 inhibition.

Antidiarrhoeal and Anti-peristaltic agents: Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Antimuscarinics: Concomitant use of antimuscarinics or medications with muscarinic action, e.g., atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Neuromuscular Blocking Agents: The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Quinidine: Quinidine can inhibit the analgesic effect of codeine.

Mexiletine: Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Metoclopramide, cisapride and domperidone: Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Cimetidine: Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naxolone: Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Interference with laboratory tests: Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy:
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 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 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).

Breast-feeding:
This product should not be used during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Fertility:
See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Patients may become dizzy and sedated with Nurofen Plus Tablets. Rare side effects may include convulsions, hallucinations, blurred or double vision and orthostatic hypotension (see section 4.8). 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 and Codeine at OTC doses (maximum 1200mg ibuprofen per day), in short-term use. 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.

Adverse events which have been associated with Ibuprofen and Codeine are given below tabulated by System Organ Class (SOC) 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	Very rare	Haematopoietic disorders[1]	

Lymphatic System Disorders		
Immune system disorders	Uncommon	Hypersensitivity reactions with urticaria and pruritus[2]
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)[2]
Metabolism and Nutrition Disorders	Not known Not known	Decreased appetite Hypokalaemia[11]
Psychiatric Disorders	Not known	Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares.
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[3]
	Not known	Dizziness, drowsiness, convulsion, intracranial pressure increased, dyskinesia
Eye Disorders	Very rare	Vision blurred
	Not known	Diplopia
Ear and Labyrinth disorders	Not known	Vertigo
Cardiac Disorders	Very rare	Cardiac failure and oedema[4].
	Not known	Bradycardia, palpitations, Kounis syndrome
Vascular Disorders	Very rare	Hypertension[4]
	Not known	Orthostatic hypotension
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea[2] Respiratory depression, cough suppression
Gastro-intestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia .Exacerbation of colitis and Crohn's disease, gastritis[5,6].
	Rare	Diarrhoea, flatulence, constipation and vomiting.
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis[7]. Mouth ulceration.
	Not known	Dry mouth, pancreatitis
Hepatobiliary Disorders	Very rare	Liver disorder[8],
	Not known	Biliary colic, sphincter of Oddidysfunction
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash[2]
	Very rare	Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrosis)[2].
	Not known	Flushing. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Musculoskeletal and Connective Tissue Disorders	Not known	Muscle rigidity
Renal and Urinary Disorders	Very rare	Acute renal failure[9]
	Not known	Ureteric colic, dysuria[10].

	Not known	Renal tubular acidosis[11]	
General and Administration Site Conditions	Not known	Hypothermia, hyperhidrosis, irritability, fatigue, malaise.	
Investigations	Very rare	Haemoglobin decreased, urea renal clearance 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.	

Drug dependence

Repeated use of Nurofen Plus can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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, nose and skin 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 pruritius, 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). 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 studies suggest that use of Ibuprofen, particularly at a high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

[5]The adverse events observed most often are gastrointestinal in nature.

[6]See Section 4.4.

[7]Sometimes fatal.

[8]Especially in long-term treatment.

[9]Especially in long-term use, associated with increased serum urea concentrations and oedema. Also includes papillary necrosis.

[10]Increased frequency, decrease in amount.

[11]Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses due to dependence on the codeine component.

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 children, ingestion of more than 400 mg/kg ibuprofen may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours. Ingestion of more than 350mg Codeine or for a child, more than 5mg Codeine per kg of bodyweight, should be considered potentially harmful. Fatalities due to codeine overdose have been reported with

intakes above 500mg. Due to the relative concentrations of each active ingredient in the product and their respective toxicity thresholds, the toxic effects of codeine in overdose would be expected to occur before those of ibuprofen.

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 gastro-intestinal irritation or bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as dizziness, drowsiness, occasionally excitation and disorientation, respiratory depression, excitability, convulsions, loss of consciousness, or coma. Co-ingestion of other sedative agents, including alcohol, may exacerbate effects on the central nervous system. Occasionally patients develop convulsions. The pupils may be pin point in size. Hypotension and tachycardia are possible but unlikely. 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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

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, including more than 350mg Codeine or for a child, more than 5mg Codeine per kg of bodyweight. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodiliators for asthma.

If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken. Any imbalance in electrolyte levels should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Ibuprofen combinations; **ATC Code:** N02 AJ08
Ibuprofen is an NSAID which acts peripherally, inhibiting prostaglandin synthesis and the action of chemical mediators of pain. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation. 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 suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics 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).

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

The combination of the two drugs is appropriate from a pharmacokinetic viewpoint; the tablet exhibits normal release characteristics for both active substances.

Ibuprofen is rapidly absorbed from the gastrointestinal tract following administration and is rapidly distributed throughout the whole body. It is extensively bound to plasma proteins and diffused into the synovial fluid. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after one to two hours. These times may vary with different dosage forms.

The half-life of ibuprofen is about two hours.

Codeine phosphate is well absorbed after oral administration, producing peak plasma concentrations in about one hour. The plasma half-life is approximately three hours, excretion being mainly in the urine.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Sodium starch glycolate Type A
Hypromellose
Pregelatinised maize starch

Film coating
Hypromellose
Talc
Opaspray white M-1-7111B
(containing: Hypromellose and titanium dioxide (E171))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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 (250 micron PVC/40gsm PVDC heat sealed to aluminium foil) containing 6, 12 or 24 tablets (OTC pack sizes).

Blister packs (250 micron PVC/40gsm PVDC heat sealed to aluminum foil) containing 32 or 48 tablets (POM pack sizes).

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

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

December 2024