SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Plus

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituents:

Ibuprofen Ph Eur	200.0 mg
Codeine phosphate Ph Eur	12.8 mg

3 PHARMACEUTICAL FORM

Tablet

4.1 Therapeutic indications

Nurofen Plus (which contains codeine) is indicated in patients older than 12 years of age for the short term treatment of acute, moderate pain (such as rheumatic and muscular pain, backache, migraine, headache, neuralgia, period pain and dental pain) which is not considered to be relieved by other analgesics such as paracetamol, ibuprofen or aspirin alone.

4.2 Posology and method of administration

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

Posology:
Recommended dosage:

Adults, the elderly and children over 12 years of age:

One or two tablets every four to six hours.

Children aged 12-18 years:
One or two tablets every four to six hours.

Children under 12 years:
Nurofen plus (which contains Codeine) 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 and 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.

Leave at least four hours between doses and do not take more than 6 tablets (1200mg) in any 24 hour period.

The maximum recommended daily dose should not be exceeded

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.

For short term use only. Codeine should be used at the lowest effective dose for the shortest period of time necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3 days.

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 Ibuprofen, Codeine or to any of the constituents listed in section 6.1.

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

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

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe hepatic failure, renal failure or heart failure (See section 4.4, Special warnings and precautions for use).

Last trimester of pregnancy (See section 4.6 Pregnancy and lactation).

In women during breastfeeding (see section 4.6)

Respiratory depression.

Chronic constipation

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

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 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 control symptoms (see GI and cardiovascular risks below).

The elderly are at increased frequency of adverse reactions to NSAIDS, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

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

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:
Systemic lupus erythematosus and mixed connective tissue disease due to increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

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

Hepatic:
Hepatic dysfunction (See section 4.3 and Section 4.8).

Cardiovascular and cerebrovascular effects:

Cases of Kounis syndrome have been reported in patients treated with ibuprofen containing products such as with Nurofen Plus Tablets. 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.

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

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

Nurofen Plus tablets should be used with caution in those with hypotension and/ or hypothyroidism. The tablets should be used with caution in patients with raised intracranial pressure or head injury.

Gastrointestinal effects:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (See section 4.8 Undesirable effects).

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of 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.

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 gastrotoxicity, ulceration or bleeding, such as oral corticosteroids, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as Acetylsalicylic Acid (aspirin) (see section 4.5 Interactions).

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

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 syndrome), and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occured within the first month. If signs and suggestive of these reactions appear, ibuprofen should be withdrawn immediately, and an alternative treatment considered (as appropriate).

Sleeping disorder where your body stops and starts your breathing in a way that disrupts your sleep: 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 opioid dosage using best practices for opioid taper

Increased sensitivity to pain: Hyperalgesia has been reported with the use of opioids, particularly following long-term use and/or at high doses. Hyperalgesia may resolve with opioid dose reduction, discontinuation, or switching to a different opioid

Masking of symptoms of underlying infections

This medicinal product 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 this medicine is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Excipients

- This medicine contains less than 1 mmol sodium (23mg) per dose, that is to say essentially 'sodium-free'.

Do not take concurrently with any other Codeine containing compounds.
Care is advised in the administration of Codeine to patients with hypotension, hypothyroidism, adrenocortical insufficiency, shock, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of peptic ulcer or convulsions and also in patients with a history of drug abuse.

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.

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. 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.

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.

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

If you are pregnant or are being prescribed medicines by your doctor, seek this advice before taking this product. Care is advised in the administration of this product in patients with severe renal or severe hepatic impairment (hepatic disease).

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 summarised 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%-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 ultrarapid 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.

The label will include:

Front of pack:

- Can cause addiction
- For three days use only

Back of pack:

- List of indications as agreed in 4.1 of the SmPC
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse

Read the enclosed leaflet before taking this product.
Do not take if you

- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
- are breastfeeding

Speak to a pharmacist or your doctor before taking this product if you

- have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, liver, heart, kidney or bowel problems

- are a smoker
- are pregnant

If symptoms persist or worsen, consult your doctor.

The leaflet will include:

- Headlines section (to be prominently displayed at the start of the PIL)
  - This medicine can only be used for …….(indications)
  - You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice
  - This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it
  - If you take this medicine for headaches for more than three days it can make them worse

- Section 2: Before taking – Do not take
  - This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it
  - If you take a painkiller for headaches for more than three days it can make them worse

- Section 3: Dosage
  - (In the dosage warning section): This medicine should not be taken for more than 3 days. If the pain does not improve after 3 days, talk to your doctor for advice.
  - This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

- Section 4: Side effects
  - Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday – Friday) or fill in a paper form available from your local pharmacy.

  - How do I know if I am addicted?
    If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:
    - You need to take the medicine for longer periods of time
    - You need to take more than the recommended dose
    - When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again

4.5 Interaction with other medicinal products and other forms of interaction

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

Ibuprofen should be avoided in combination with:

Acetylsalicylic Acid (Aspirin): Unless low-dose acetylsalicylic acid (aspirin) (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (See section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose *Acetylsalicylic Acid (*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).

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).

Serotonergic drugs: Serotonin syndrome has been reported during concomitant use of serotonergic drugs including triptans, selective serotonin-reuptake inhibitors (SSRIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), and tricyclic antidepressants, with opioids at recommended dosages

Ibuprofen should be used with caution in combination with:

Anticoagulants: 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 effect of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of an ACE inhibitor or Angiotens II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (See section 4.4 Special warnings).

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 a potential for an increase in plasma 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 hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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

- **Monoamine Oxidase Inhibitors (MAOIs):** 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.
- **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 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).
- **Diuretics and Anti-hypertensives:** The hypotensive actions of diuretics and anti-hypertensive agents may be potentiated when used concurrently with opioid analgesics.
- **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.

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

From the 20th week of pregnancy onward, Nurofen Plus 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 constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Nurofen Plus should not be given unless clearly necessary. If Nurofen Plus 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Nurofen Plus for several days from gestational week 20 onward. Nurofen Plus 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 persistent 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 at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Nurofen Plus is contraindicated during the third trimester of pregnancy (See section 4.3).

Breast Feeding:

Codeine 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 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:

There is limited 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.

4.7 Effects on ability to drive and use machines

Patient may become dizzy or 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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When taking this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

    - The medicine has been taken to treat a medical or dental problem and
    - You have taken it according to the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Hypersensitivity reactions have been reported and these may consist of:

a) Non-specific allergic reactions and anaphylaxis.

b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea.

c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme). Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headache can make them worse.

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200mg Ibuprofen per day), for short-term use. In the treatment of chronic conditions, 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.

Cardiovascular and Cerebrovascular:
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

System Organ Class	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and Pruritus[2]
	Very rare	Severe hypersensitivity reactions including facial, tongue and throat swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock)[2]
Metabolism and Nutrition Disorders	Not known	Decreased appetite, hypokalaemia[3]
Psychiatric Disorders	Not known	Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[4]
	Not known	Dizziness, drowsiness, convulsion, Intracranial

		pressure increased, headache, dyskinesia.
Eye Disorders	Not known	Vision blurred, diplopia
Ear and Labyrinth disorders	Not known	Vertigo
Cardiac Disorders	Not known Not known	Cardiac failure, oedema, bradycardia, palpitations[5] Kounis syndrome
Vascular Disorders	Not known	Hypertension, orthostatic hypotension[5]
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea[2], respiratory depression, cough suppression
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia[4,6]
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis[7]. Mouth ulceration and gastritis. Exacerbation of ulcerative colitis and Crohn's disease[8]. Dry mouth.
	Not known	Dry mouth, pancreatitis
Hepatobiliary Disorders	Very rare	Liver disorder
	Not known	Biliary colic, sphincter of Oddi dysfunction
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes[2]
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnsons

		Syndrome, and toxic epidermal necrolysis[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], Renal tubular acidosis[3]
General and Administration Site Conditions	Not known	Hypothermia, hyperhidrosis, irritability, fatigue, malaise
Investigations	Very rare	Haemoglobin decreased

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] Renal tubular acidosis and hypokalaemia have been reported following chronic overdose of the ibuprofen component, due to dependence on the codeine component.

[4] 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). 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 (see section 4.4).

[5] Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) (see section 4.4).

[6] The most commonly-observed adverse events observed are gastrointestinal in nature.

[7] Sometimes fatal, particularly in the elderly.

[8] See section 4.4.

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

[10] Increased frequency, decrease in amount.

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).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Symptoms of overdose with ibuprofen include;

In children ingestion of more than 400 mg ibuprofen per kg of bodyweight may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours. Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. 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.

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 5 mg codeine per kg of bodyweight. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

Symptoms of overdose with codeine include;

Nausea and vomiting are prominent features. Respiratory depression, excitability, convulsions, hypotension drowsiness, unresponsiveness to stimuli, pinpoint pupils, sweating, hyperventilation, increased pulse rate, shallow respiration, mixed metabolic and respiratory acidosis, increased plasma codeine levels and loss of consciousness may occur with large codeine overdose.

The stomach should be emptied. If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Give naloxone if coma or respiratory depression is present. Naloxone is 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. Imbalance in electrolyte levels should be considered.

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Ibuprofen, combinations; **ATC Code:** M01 AE51

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

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

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no

firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

The elimination half-life of both ibuprofen and codeine is approximately three hours, and both drugs are given three to fours 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

Tablet core:

Microcrystalline cellulose, Sodium starch glycollate, Starch pregelatinised, Hypromellose

Film coating:

Hypromellose Ph Eur

Opaspray White M-1-17111B

Talc Ph Eur

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a dry place below 25ºC.

6.5 Nature and contents of container

Blister packs containing 6, 8, 12, 16, 18, 24 or 32 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Healthcare (UK) Ltd
Slough
SL1 4AQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 00063/0376

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 May 1994 / 19 September 2008

10 DATE OF REVISION OF THE TEXT

29/04/2026