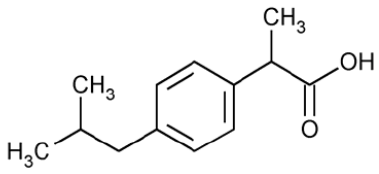
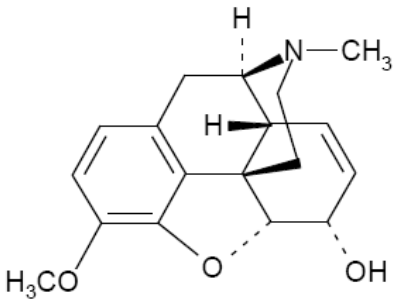
PRODUCT INFORMATION

i) Name of the medicine:

NUROFEN PLUS
ibuprofen 200mg and codeine phosphate hemihydrate 12.8mg





$.H_3PO_4 \cdot {}_{1/2}H_20$

Ibuprofen
CAS: 15687-27-1
Molecular formula: $C_{13}H_{18}O_2$.
MW:206.3

Codeine
CAS: 41444-62-6
Molecular formula: $C_{18}H_{21}NO_3.H_3PO_4.1/2\ H_2O$.
MW:406.4

Nurofen Plus tablets are gluten-free and lactose-free.

ii) Description

Ibuprofen: Chemical name: 2-(4-Isobutylphenyl) propionic acid. It is a white or almost white powder or crystals with a characteristic odour. Practically insoluble in water, soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone; soluble in aqueous solutions of alkali hydroxides and carbonates.

Codeine phosphate hemihydrate: Chemical name: (5R,6S)-7, 8-didehydro-4,5-epoxy-3-methoxy-N-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate. It is a small, colourless, odourless crystal or a white, odourless crystalline powder. Codeine phosphate is soluble in four parts water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

A white capsule-shaped tablet, containing ibuprofen 200mg and codeine phosphate hemihydrate12.8mg. Also containing microcrystalline cellulose, sodium starch glycollate, hypromellose, pregelatinised maize starch, talc and Opaspray white colouring.

iii) Pharmacology:

Actions:

It is thought that ibuprofen produces an anti-inflammatory effect at least in part by inhibiting prostaglandin synthetase. Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both animal and human studies.

Codeine phosphate hemihydrate is a narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be largely due to its biotransformation to morphine.

Pharmacokinetics:

Ibuprofen

Absorption. Ibuprofen is well absorbed after oral administration with peak serum levels occurring after 1 to 2 hours.
Distribution. Apparent volume of distribution is 0.14L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant rabbits and rats. It is not known if the drug enters the cerebrospinal fluid.
99% of ibuprofen is protein bound. The high protein binding of the drug should be borne in mind when prescribing ibuprofen together with other protein bound drugs that bind to the same site on human serum albumin.
Metabolism. 90% of ibuprofen is metabolised in the liver to produce two major metabolites, a hydroxylated and carboxylated compound.
Excretion. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney with 95% of the administered dose eliminated in the urine within four hours of ingestion.
The elimination half-life of ibuprofen is in the range 1.9 to 2.2 hours.

Codeine

Absorption: Codeine is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached one hour after oral administration. Onset of action occurs in 15 to 30 minutes and analgesia is maintained for 4 to 6 hours.
Distribution: Codeine is rapidly distributed to skeletal muscles, kidneys, liver, gastrointestinal tract, lungs, spleen and brain. It crosses the placenta and is distributed in low levels in breast milk.
Metabolism: Codeine is metabolised mainly in the liver. The major metabolic pathway involves glucuronidation of codeine to codeine-6-glucuronide. Codeine can also undergo O- and N-demethylation catalysed by CYP2D6 and CYP3A4 respectively. About 10% of an administered dose of codeine is converted by O-demethylation to morphine, which subsequently undergoes glucuronidation to morphine-3 or morphine-6 glucuronide, or N-demethylation to normorphine. Approximately 8% of the general Australian population cannot convert codeine to the active metabolite morphine as they are deficient in the CYP2D6 enzyme. These patients are likely to obtain reduced pain relief from codeine. Codeine is also converted by N-demethylation to norcodeine, which subsequently undergoes glucuronidation to norcodeine glucuronide or O-demethylation to normorphine.
Excretion: Codeine is excreted mainly by the kidneys. Of the excreted material in the urine 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine, and 10-20% is free or conjugated norcodeine. The plasma half-life of codeine is 2 to 4 hours. Only traces of codeine and its metabolites are found in the faeces

iv) Clinical trials

This section is not applicable

v) Indications

The temporary relief of strong pain and/or inflammation associated with headache (including migraine and tension headache), period pain, dental pain, back pain, neuralgia, rheumatic and arthritic pain, muscular pain.

v) Contraindications

Known hypersensitivity to ibuprofen, codeine or other opioid analgesics, or any of the excipients.

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

Active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). As with other non-steroidal antiinflammatory agents, ibuprofen should not be used in active gastrointestinal bleeding or in the presence of peptic ulceration.

Respiratory depression, chronic constipation and active alcoholism.

Diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).

Use with concomitant NSAIDs, including cyclo-oxygenase-2 specific inhibitors - increased risk of adverse reactions

Heart or renal problems. (see Precautions).

Severe hepatic impairment (see Precautions)

During the last trimester of pregnancy (see Precautions).

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

Use of codeine containing products is contraindicated in women during breast feeding (see Precautions).

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

In paediatric patients aged under 12 years.

In all paediatric patients 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 Precautions).

Treatment of perioperative pain in setting of coronary artery bypass surgery (CABG)

vii) Precautions

Effects on 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.

Use in Pregnancy
Category C: Inhibition of prostaglandin synthesis by ibuprofen may adversely affect pregnancy and/or the embryo/foetal development. During the first and second trimester of pregnancy, this product should not be given unless clearly necessary, and is contraindicated in the third trimester.

During the third trimester, all prostaglandin synthesis inhibitors may expose the foetus to cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction, which may progress to renal failure with oligohydramnios. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to possible prolongation of bleeding time and inhibition of uterine contractions, which may result in delayed or prolonged labour.

Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. The use of codeine may prolong labour. Administration of codeine during labour may cause respiratory depression in the newborn infant.

Use in Lactation
The use of Nurofen Plus during breastfeeding is contraindicated.

In limited studies, ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely. Codeine is excreted in breast milk and should not be used during breastfeeding. 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. If symptoms of opioid toxicity develop in either the mother or the infant, then immediate medical care should be sought and all codeine containing medicines should be stopped. A fatal case of opioid toxicity has been reported in a newborn whose mother was taking codeine and happened to be an ultra-rapid metaboliser.

Paediatric use
Do not give to children under 12 years (see Contraindications).

Use in the elderly
Adverse effects may have more serious consequences in the elderly, and they may be more susceptible to the CNS depressant effects of opioids.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see below).

Gastrointestinal
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 Adverse effects).

Gastrointestinal bleeding, ulceration and perforation which can be fatal, has been reported with all NSAIDs at any time 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 and patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See Contraindications) and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly the elderly, patients with a history of gastrointestinal bleeding or perforation or peptic ulcer haemorrhage related to previous NSAID therapy should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Care is advised in the administration of NUROFEN PLUS to patients with obstructive bowel disorders, recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of peptic ulcer or convulsions.

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 Interactions with Other Medicines).

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

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

SLE and mixed connective tissue disease
Use of ibuprofen in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease can increase the risk of aseptic meningitis.

Hepatic
As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.

Nurofen Plus should be administered with caution in patients with hepatic impairment. Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the steps to take should these signs and/or symptoms occur.

Renal
Renal impairment as renal function may deteriorate, especially in dehydrated paediatric patients (see Contraindications and Undesirable Effects).

Cardiovascular and cerebrovascular effects
Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.
Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.

Nurofen Plus should be administered with caution in patients with hypertension or fluid retention (see Contraindications – heart failure).

Dermatological
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 Adverse Effects). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Nurofen Plus use should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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, swallowing breathing, small pupils, nausea, vomiting, constipation, and lack of appetite. In several 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 2.0%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children: There have been reports in the published literature that **c**odeine 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 Contraindications). 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.

Other precautions

As with other drugs of this class, ibuprofen may mask the usual signs of infection. Codeine may also obscure the diagnosis or the course of gastrointestinal diseases. NUROFEN PLUS should therefore be administered with caution in such situations.

NUROFEN PLUS should be administered with caution in patients who have recently had gastrointestinal surgery, as codeine may reduce gastrointestinal motility.

NUROFEN PLUS should be administered 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.

Physical and/or psychological dependence may occur following prolonged administration of codeine. Tolerance may also develop following prolonged administration and irritability and restlessness may be experienced when the tablets are stopped

NUROFEN PLUS should be administered with caution in patients with prostatic hypertrophy since codeine may cause urinary retention.

Care is advised in the administration of NUROFEN PLUS to patients with adrenocortical insufficiency and also in patients with a history of drug abuse.

The effect of ability to drive and use machinery

Codeine may cause drowsiness.

Opioid analgesics can impair mental function and cause blurred vision and dizziness. Rare side effects may include convulsions, hallucinations, blurred or double vision and orthostatic hypotension. Patients should be advised not to drive or operate machinery.

viii) Interactions with Other Medicines

Nurofen Plus should be avoided in combination with:

Aspirin. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, no clinically relevant effect is considered to be likely for occasional ibuprofen use. .

Other NSAIDs: Including cyclooxygenase-2-selective inhibitors. Avoid the use of two or more NSAIDs as this may increase the risk of adverse effects.

Nurofen Plus should be used with caution in combination with:

Anticholinergics. Concurrent use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention.

Anticoagulants. Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin. NUROFEN PLUS should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

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 increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

ACE inhibitors, diuretics and other antihypertensives.
Ibuprofen, like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of diuretics.

Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension. NSAIDs may diminish the effects of antihypertensives and diuretics. Diuretics can increase the risk of nephrotoxicity of NSAIDs

The combined use of the three classes of drugs, diuretics, an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or cyclooxygenase-2 (COX-2) inhibitor) all at the same time increases the risk of renal impairment. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.
Antiperistaltic antidiarrhoeals (including kaolin, pectin, loperamide). Concurrent use of these agents with codeine may increase the risk of severe constipation

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs). Increased risk of gastrointestinal bleeding (see Precautions)

Cardiac glycosides. NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Central nervous system depressants. Codeine may potentiate the effects of CNS depressants.

Ciclosporin. An increased risk of nephrotoxicity

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

Corticosteroids. An increased risk of gastrointestinal ulceration or bleeding may occur with corticosteroids (see Precautions).

Drugs that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents. Can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.

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

Lithium. Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

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

Methotrexate. NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction in the clearance of methotrexate may occur. Use of high doses of methotrexate concomitantly with NSAIDs should be avoided. At low doses of methotrexate, caution should be used if ibuprofen is administered concomitantly.

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

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Moclobemide: Risk of hypertensive crisis.

Monoamine oxidase inhibitors (MAOIs). Concurrent administration or use within 14 days of ceasing monoamine oxidase inhibitors may enhance the potential respiratory depressant effects of codeine. 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.

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

NSAIDs and aspirin. Concurrent use of ibuprofen with aspirin or other NSAIDs can lead to increased gastrointestinal adverse effects.

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

Opioid analgesics. Concurrent use of codeine and other opioid receptor agonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur.

Probenecid and phenytoin. Interactions may also occur with probenecid, antidiabetic medications and phenytoin.

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

Quinidine. Quinidine can inhibit the analgesic effect of codeine

Tacrolimus. Possible increased risk of nephrotoxicity when NSAIDs are given with

Tacrolimus.

Tranquillizers, sedatives and hypnotics. Codeine may potentiate the effects of these drugs.

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 (+) haemophiliacs receiving concurrent treatment with Zidovudine and ibuprofen.

Incompatibilities: Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeine phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide. Acetylation of codeine phosphate by acetylsalicylic acid (aspirin) has occurred in solid dosage forms containing the two drugs, even at low moisture levels.

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. Opoids 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.

ix) Adverse effects:

The most commonly observed adverse events are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding which is dependent on the dosage range and duration of treatment.

Side effects from codeine are theoretical warnings based on drug class. No clinical data is available to determine frequency.

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 list of the following adverse events relates to those experienced with ibuprofen and codeine at OTC doses (maximum of 1200mg ibuprofen per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

Adverse events which have been associated with ibuprofen and codeine are given below, tabulated by System Organ Class (SOC) and frequency.

The frequencies of adverse effects are defined as follows:
Very common: *≥1/10*
Common: *≥1/100, <1/10*

Uncommon: *≥1/1,000, <1/100*
Rare: *≥1/10,000, <1/1,000*
Very Rare: *<1/10,000,* including isolated reports.
Not known: cannot be estimated from the available data.

Within each frequency grouping, adverse events are presented in order of decreased seriousness.

System Organ Class	**Frequency**	**Adverse Events**
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1], alveolitis, pulmonary eosinophilia, pancreatitis, haemoglobin decreased, platelet aggregation[2]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus[3]
	Very rare	Severe hypersensitivity reactions, including swelling face, swollen tongue and laryngeal oedema, dyspnoea, apnoea and tachycardia, (anaphylaxis, angioedema or severe shock)[3]
Metabolism and nutrition disorders	Not known	Decreased appetite
Psychiatric Disorders	Not known	Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares, irritability
Nervous System Disorders	Common	Drowsiness
	Uncommon	Headache, dizziness
	Very rare	Aseptic meningitis[4], nervousness, tinnitus, depression, insomnia, disturbance in attention, affect lability, convulsions.
	Not known	Intracranial pressure increased, dyskinesia, miosis
Eye Disorders	Very rare	Vision blurred, amblyopia, visual impairment[5]
	Rare	Dry eye
	Not known	Diplopia
Ear and Labyrinth Disorders	Rare	Hearing impaired
	Not known	Vertigo
Cardiac Disorders	Rare	Palpitations[6]
	Not known	Cardiac failure, oedema, bradycardia,
Vascular Disorders	Rare	Cerebrovascular accident[6], hypotension, cardiac failure congestive[7]
	Not known	Hypertension, orthostatic hypotension[6]
Respiratory, Thoracic and Mediastinal Disorders	Rare	Rhinitis
	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea[3]

System Organ Class	Frequency	Adverse Events
		Respiratory depression, cough suppression
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea, dyspepsia
	Rare	Diarrhoea, flatulence, constipation, vomiting, Dry mouth, gingival ulceration
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis[8]. Mouth ulceration, gastritis. Exacerbation of ulcerative colitis and Crohn's disease[9]
Hepatobiliary Disorders	Very rare	Liver disorder[10]
	Not known	Biliary colic
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash[3]
	Rare	Skin exfoliation, alopecia, dermatitis exfoliative, photosensitivity reaction, rash maculo-papular,hyperhidrosis
	Very rare	Bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis[3]
	Not known	Flushing
Musculoskeletal and connective tissue Disorders	Not known	Muscle rigidity
Renal and Urinary Disorders	Very rare	Acute renal failure[11]
	Not known	Renal colic, , dysuria[12]
General Disorders and Administration Site Conditions	Not known	Hypothermia, fatigue, malaise
Investigations	Very rare	Haemoglobin decreased

Description of Selected Adverse Reactions

[1] Examples include anaemia, neutropenia, aplastic anaemia, haemolytic anaemia, eosinophilia, reduction of haemoglobin and haematocrit leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising

[2] Reversible.

[3] Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of

a) non-specific allergic reactions and anaphylaxis
b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea

c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme). Severe shock syndrome may be characterised by abdominal pain, fever, shivering, nausea and vomiting. Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions.

[4] The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSID related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff, neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus and mixed connective tissue disease).

[5] Includes changes in visual colour perception

[6] 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 (e.g. myocardial infarction or stroke), (see section "Precautions").

[7] In patients with compromised cardiac function.

[8] Sometimes fatal, particularly in the elderly.

[9] See section "Precautions"

[10] Especially in long term treatment, including hepatotoxicity, hepatitis, jaundice, alterations of hepatic function tests, pancreatitis, duodenitis, oesophagitis, hepato-renal syndrome, hepatic necrosis, hepatic insufficiency

[11] Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis. Ibuprofen may cause cystitis and haematuria, interstitial nephritis, nephrotic syndrome, oliguria, tubular necrosis, glomerulonephritis, alteration in the renal function test, polyuria, anaphylaxis.

[12] Increased frequency, decrease in amount.

x) Dosage and administration:

Dosage:

Adults and children 12 years and over:

Initial dose two tablets taken with fluid, then one or two tablets every 4 to 6 hours when necessary. Maximum 6 tablets in a 24-hour period.
Nurofen Plus should not be used for more than three days at a time unless on medical advice, in which case the patient should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Children:
Do not give to children under 12 years.

xi) Overdosage:

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- The symptoms of overdose with ibuprofen include nausea, vomiting, abdominal pain, diarrhoea (rarely), headache, dizziness, drowsiness, nystagmus, vertigo, blurred vision, tinnitus and rarely, hypertension, metabolic acidosis, convulsions, excitation, disorientation, coma, renal failure, liver damage, hypotension, respiratory depression, cyanosis and loss of consciousness. Exacerbation of asthma is possible in asthmatics.

Nausea and vomiting are prominent features of codeine overdose. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose. Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pinpoint in size. Hypotension and tachycardia are possible.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26.

xii) Presentation and storage conditions

Dosage form
White capsule-shaped tablets marked ‘N+’on one side.

Quantity, proportion or strength of each therapeutically active ingredient
ibuprofen 200mg and codeine phosphate hemihydrate12.8mg

Container type
Aluminium blister packed in a carton

Pack sizes
Packs of *4, *6, *12, *24 and 30 tablets

Storage conditions
Store below 25 degrees Celsius.

xiii) Name and address of sponsor:

Reckitt Benckiser
Sydney NSW
Australia

xiv) Poison Schedule of the medicine

Nurofen Plus in packs *4, *6, *12, *24 and 30 tablets are S4 (Prescription Only Medicine)

xv) Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG)

17 February 2005

xvi) Date of most recent amendment

June 2017

*Not available in Australia