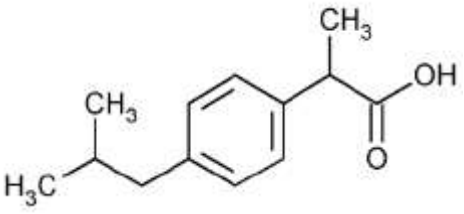
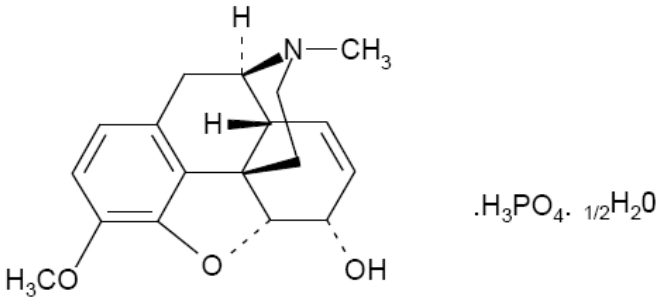
PRODUCT INFORMATION

i) Name of the medicine:

NUROFEN PLUS
ibuprofen 200mg and codeine phosphate 12.8mg





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: 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 12.8mg. 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 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.

Hypersensitivity (eg, asthma, rhinitis, angioedema, broncho-spasm or urticaria) to aspirin or other non- steroidal antiinflammatory drugs.

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

During the last trimester of pregnancy

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 embyro/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
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. The use of NUROFEN PLUS tablets should be avoided, if possible during lactation.

Paediatric use
Not recommended for children under 12 years.

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 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 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, patient 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.

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
NUROFEN PLUS should be administered with caution in patients with hepatic dysfunction

Renal
In patients with renal impairment, renal function should be monitored since it may deteriorate following the use of any NSAID.

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, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the 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).

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.

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.

Codeine may cause drowsiness, those affected should not 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.

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 Warnings)

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

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

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. Codeine may antagonise the effects of metoclopramide on gastrointestinal motility.

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.

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.

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.

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.

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

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.

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.

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.

ix) Adverse effects:

Ibuprofen:
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.

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) c) Assorted skin disorders, including rashes of various types, pruritius, urticaria, purpura, angioedema and more rarely bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long term treatment, additional adverse effects may occur.

Hypersensitivity reactions
Uncommon: Hypersensitivity reactions with urticaria and pruritius
Very rare: severe hypersensitivity reactions. Symptoms could be facial, tongue and larynx swelling, dyspnoea, apnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock - syndrome may be characterised by abdominal pain, fever, shivering, nausea and vomiting.

Exacerbation of asthma and bronchospasm.

Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions

Gastrointestinal disorders
The most commonly observed adverse events are gastrointestinal in nature.
Uncommon: abdominal pain, nausea, dyspepsia
Rare: Diarrhoea, flatulence, constipation and vomiting
Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.

Exacerbation of ulcerative colitis and Crohn's disease

Gastric pyrosis.

Nervous System
Uncommon: Headache
Very rare: Aseptic meningitis - single cases have been reported
Very rare: Dizziness, nervousness, tinnitus, depression, drowsiness, insomnia, irritability, difficulty in concentrating, emotional instability, convulsions, auditory and visual problems

Renal
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Ibuprofen may cause cystitis and haematuria, interstitial nephritis, nephrotic syndrome, oliguria, tubular necrosis, glomerulonephritis, alteration in the renal function test, polyuria,

Liver
Very rare: liver disorders, especially in long term treatment, including hepatotoxicity, hepatitis, jaundice, alterations of hepatic function tests, pancreatitis, duodenitis, oesophagitis, hepato-renal syndrome, hepatic necrosis, hepatic insufficiency.

Haematological
Very rare: Haematopoietic disorders (anaemia, neutropenia, aplastic anaemia, haemolytic anaemia, eosinophilia, reduction of haemoglobin and haematocrit leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). Reversible platelet aggregation, alveolitis, pulmonary eosinophilia, pancreatitis

Dermatological
Uncommon: Various skin rashes
Very rare: Severe forms of skin reactions such as bullous reactions including Stevens Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
Rarely skin peeling, alopecia, exfoliative dermatitis, photosensitive dermatitis, maculopapular rash

Immune System
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.

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).

Rarely: cerebrovascular accidents, hypotension, congestive cardiac insufficiency in patients with compromised cardiac function, palpitations.

Ocular:
Very rare: Blurred vision, changes in visual colour perception, toxic amblyopia, episodes of ocular alteration with consequent visual disorders.

Other:
Effect on the endocrine system and on the metabolism, reduction in appetite.
Rarely: dryness of the eyes and mouth, gingival ulcers, rhinitis, hearing disturbances

Side effects of codeine include constipation, respiratory depression, cough suppression, nausea, vomiting, constipation, drowsiness, confusion, restlessness, changes of mood and vertigo, Dry mouth, sweating, facial flushing, hypothermia, increased Intracranial pressure, bradycardia, palpitations, orthostatic hypotension, myosis, micturition, ureteric spasm, biliary spasm, urticaria, pruritis.

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.

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.

Children:

Not recommended for 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, headache, dizziness, drowsiness, nystagmus, blurred vision, tinnitus and rarely, hypertension, metabolic acidosis, renal failure and loss of consciousness. Nausea and vomiting are prominent features of codeine overdose. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose.

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+'.

Quantity, proportion or strength of each therapeutically active ingredient
ibuprofen 200mg and codeine phosphate 12.8mg

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
44 Wharf Road
West Ryde NSW 2114
Australia

xiv) Poison Schedule of the medicine
Packs of 4, 6, 12, 24 and 30 tablets are S3 (Pharmacist Only Medicine)

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

17 February 2005

xvi) Date of most recent amendment
07 November 2012