New Zealand Data Sheet

NUROFEN PLUS
Ibuprofen 200mg & Codeine phosphate 12.8mg film-coated capsule shaped tablets

COMPOSITION:

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.

NUROFEN PLUS tablets are gluten-free and lactose-free.

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.

\[
\text{Ibuprofen} \quad \text{CAS: } 15687-27-1 \\
\text{Molecular formula: } C_{13}H_{18}O_2. \\
\text{MW: 206.3}
\]

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

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 ibuprofen enters the cerebrospinal fluid. 99% of ibuprofen is protein bound. The high protein binding of ibuprofen should be borne in mind when prescribing ibuprofen together with other protein bound medicines 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.

**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, and muscular pain.

**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 effects

Heart or renal problems. (See Precautions).

Severe renal failure (glomerular filtration below 30 mL/min).

Severe hepatic failure. (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 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).

**WARNINGS AND 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**
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 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**
NUROFEN PLUS should be administered with caution in patients with hepatic dysfunction

**Renal**
Renal impairment as renal function may deteriorate; especially in dehydrated paediatric patients (see Contraindications and Adverse Events).

**Aseptic meningitis**
Aseptic meningitis has been reported only rarely, usually in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

**Haematological monitoring**
Blood dyscrasias have been rarely reported. Patients on long term therapy with ibuprofen should have regular haematological monitoring.

**Coagulation defects**
Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulation therapy.

**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.

Epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg/daily) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall epidemiological studies do not suggest that low dose ibuprofen (< 1200 mg/daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for
cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

There is no evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular events associated with NSAID use.

**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:

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>African/Ethiopian</td>
<td>29%</td>
</tr>
<tr>
<td>African American</td>
<td>3.4% to 6.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2% to 2.0%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6% to 6.5%</td>
</tr>
<tr>
<td>Greek</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hungarian</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northern European</td>
<td>1.0 to 2.0%</td>
</tr>
</tbody>
</table>

**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 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.

**Effects on ability to drive and use machinery**

Codeine may cause drowsiness. Opioid analgesics can impair mental function and cause blurring of 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.

Following treatment with ibuprofen, the reaction time of patients may be affected. NSAIDs may cause dizziness, drowsiness, fatigue and visual disturbances. If affected, patients should not drive or operate machinery.

**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.
**Antidiarrhoal and antiperistaltic agents:** Concurrent use of codeine with antidiarrhoal 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.

**Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs).**

Increased risk of gastrointestinal bleeding (see Precautions).

**Cardiac glycosides:** NSAIDs may exacerbate cardiac failure, reduce GRF 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.

**Naxolone.** Naxolone 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 medicines.

**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. 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.

**ADVERSE EFFECTS:**

The list of the following adverse events relates to those experienced with ibuprofen and codeine at OTC doses (maximum of 1200mg ibuprofen per day), in 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. Frequencies are defined as:

- Very common: $\geq 1/10$
- Common: $\geq 1/100, <1/10$
- Uncommon: $\geq 1/1,000, <1/100$
- Rare: $\geq 1/10,000, <1/1,000$
- 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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Haematopoietic disorders$^1$</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity with urticarial and pruritus</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Non known</td>
<td>Effects on the endocrine system and on metabolism, decreased appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known</td>
<td>Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares.</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nervous System disorders</td>
<td>Uncommon</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Aseptic meningitis, nervousness, tinnitus, depression, insomnia, irritability, difficulty in concentrating, emotional stability, auditory and visual problems.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dizziness, drowsiness, convulsion, intracranial pressure increased, dyskinesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Not known</td>
<td>Vision blurred diplopia (changes in visual colour perception), toxic amblyopia, episodes of ocular alteration with consequent visual disorders, dryness of the eyes.</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Not known</td>
<td>Vertigo, hearing disturbances</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Cardiac failure, oedema, bradycardia, palpitation</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Hypertension, orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Non known</td>
<td>Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea, Respiratory depression, cough suppression, rhinitis.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>Abdominal pain, nausea and dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Diarrhoea, flatulence, constipation, vomiting</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis. Mouth ulceration, ulcerative stomatitis and gastritis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Exacerbation of colitis and Crohn’s disease, dry mouth, gastric pyrosis.</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare</td>
<td>Liver disorders, especially in long-term treatment, including hepatotoxicity, hepatitis, jaundice, alterations of hepatic function tests, pancreatitis, duodenitis, esophagitis, hepato-renal syndrome, hepatic necrosis, hepatic insufficiency.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Skin rash&lt;sup&gt;2&lt;/sup&gt;, mouth and gingival ulcers.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very rare</td>
<td>Bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis, skin peeling, alopecia, exfoliative dermatitis, photosensitive dermatitis, maculopapular rash.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Muscle rigidity</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very rare</td>
<td>Acute renal failure&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
<td>Ureteric colic, dysuria&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>General and administrative site conditions</td>
<td>Not known</td>
<td>Hypothermia, hyperhidrosis, irritability, fatigue, malaise</td>
</tr>
<tr>
<td>Investigation</td>
<td>Very rare</td>
<td>Haemoglobin decreased</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Uncommon</td>
<td>Hypersensitivity reactions with urticarial and pruritus</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Very rare</td>
<td>Severe hypersensitivity reactions (facial, tongue, larynx swelling), dyspnoea, apnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock – syndrome may be characterised by abdominal pain, fever, shivering, nausea and vomiting).</td>
</tr>
</tbody>
</table>
Not known | Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea. Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions.

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 e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
  c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely bullous dermatoses (including epidermal necrolysis and erythema multiforme).

3 The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID- related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). 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, mixed connective tissue disease).

4 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).

5 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.

6 Sometimes fatal.

7 See Precautions.

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

9 Increased frequency, decrease in amount.

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

**Codeine**

Side effects of codeine include constipation, respiratory depression, cough suppression, nausea, vomiting, constipation, upper abdominal pain, biliary colic, ureteric colic, dysuria (increased frequency, decrease in amount), decreased appetite, muscle rigidity, drowsiness, confusion, restlessness, changes of mood, nightmares, headache, dyskinesia, vertigo, dry mouth, sweating, facial flushing, hypothermia, hyperhidrosis, irritability, fatigue, malaise, increased intracranial pressure, bradycardia, palpitations, orthostatic hypotension, myosis, micturition, ureteric spasm, biliary spasm, urticaria, pruritus.

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.

**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 as necessary. Maximum 6 tablets in a 24-hour period.

**Children:**
NUROFEN PLUS is not indicated for use in children under 12 years of age.

Do not use for more than 3 days at a time, except on doctor’s advice. The recommended dose should not be exceeded. Excessive use can be harmful. Codeine use can cause addiction.

**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 pin-point in size. Hypotension and tachycardia are possible.

The Poisons Information Centre can also be contacted (New Zealand 0800 764 766) for current information on the treatment of oral overdoses.

**PRESENTATION:**

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

**PHARMACEUTICAL PRECAUTIONS:**

Store below 25°C.

**MEDICINES CLASSIFICATION:**

Pharmacist Only Medicine.

**PACKAGE QUANTITIES:**

Packs of 12, 24 and 30 tablets. Not all pack sizes may be marketed.

**NAME AND ADDRESS:**

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Freephone: 0508 731 234

**DATE OF PREPARATION**

26 November 2015