

## 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 glycolate, 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. Molecular formula:  $C_{13}H_{18}O_2$ . MW:206.3. CAS: 15687-27-1. 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. Molecular formula:  $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2 H_2O$ . MW:406.4. CAS: 41444-62-6. 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.

#### 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.

**Protein binding.** 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.

**Half-life.** 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, muscular pain.

### **CONTRAINDICATIONS:**

NUROFEN PLUS is contraindicated in the following conditions:

- Known hypersensitivity to ibuprofen, codeine or other opioid analgesics, or any of the excipients.
- Hypersensitivity (eg, asthma, rhinitis or urticaria) to aspirin or other NSAIDs.
- As with other NSAIDs, 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).
- Obstructive airways disease.
- Head injuries or conditions in which intracranial pressure is raised.
- Patients at risk of paralytic ileus.
- Hepatic failure.
- Acute asthma attack.
- Severe heart failure.

### **PRECAUTIONS:**

NUROFEN PLUS should be used with caution in patients with the following conditions:

- Adrenocortical insufficiency e.g. Addison's Disease
- Myasthenia gravis
- Convulsions/convulsive disorders
- Gall bladder disease or gall stones
- Urinary tract surgery
- Reduced respiratory function or history of asthma, especially those patients who have not taken an NSAID before.
- Obstructive and inflammatory bowel disease – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- SLE and mixed connective tissue disease due to an increased risk of aseptic meningitis.

The use of NUROFEN PLUS with other NSAIDs including cyclooxygenase 2 selective inhibitors should be avoided.

NUROFEN PLUS should be administered with caution in patients with hepatic, renal or cardiac impairment. In patients with renal impairment, renal function should be monitored since it may deteriorate following the use of any NSAID.

As with other medicines 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 those with hypotension and /or hypothyroidism. The tablets should be used with caution in patients with CNS depression, since codeine may increase the risk of respiratory depression and further elevate intracranial pressure.

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

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

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

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin.

Hypersensitivity – Maculopapular rash, fever, splenomegaly and lymphadenopathy have been seen as part of a codeine hypersensitivity reaction. Bronchospasm may be precipitated by ibuprofen in patients suffering from or with a previous history of asthma or allergic disease.

Skin reactions – 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. 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 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Dependence – Taking codeine regularly for a long time can lead to addiction. Stopping treatment can result in withdrawal symptoms. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for headache can result in an overuse syndrome.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Withdrawal – Abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure. These effects can also occur in neonates exposed to codeine in utero (see use in pregnancy)

Genetic polymorphism – Codeine is metabolised to morphine by cytochrome P450 2D6. Some patients are ultra-rapid metabolisers and are at high risk of toxic opioid effects. Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

Impaired female 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 upon withdrawal of treatment.

NUROFEN PLUS should not be taken with alcohol.

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

Codeine may cause drowsiness, Do not drive or operate machinery if you are feeling drowsy.

### **Use in Pregnancy:**

NUROFEN PLUS should not be taken during the first 6 months of pregnancy except on doctor's advice. Not to be taken at all during the last three months of pregnancy.

(Category C): NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth.

Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high-dose use of Codeine prior to delivery may produce Codeine withdrawal symptoms in the neonate.

Based on animal studies and limited clinical experience there is no evidence to suggest foetal abnormalities associated with the use of codeine. However, NUROFEN PLUS tablets should be avoided during pregnancy.

### **Use in Lactation:**

NUROFEN PLUS should not be taken while breast feeding except on doctor's advice.

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 into breast milk. However with usual analgesic doses, concentrations are generally low.

However, infants of nursing mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Nursing mothers taking codeine, who are ultra-rapid metabolisers, may have higher morphine levels in their breast milk, which may lead to life-threatening or fatal side effects in nursing babies.

Signs of high morphine levels in a mother are extreme sleepiness and trouble caring for the baby.

Breastfed babies usually nurse every two to three hours and should not sleep more than four hours at a time. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice.

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

### **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. NUROFEN PLUS should only be used in patients 65 years or older after seeking medical advice.

### **Interactions with Other Medicines**

**ACE inhibitors and diuretics:** 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.

**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.

**Antihypertensives:** Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.

**Antiperistaltic antidiarrhoeals** (including kaolin, pectin, loperamide). Concurrent use of these agents with codeine may increase the risk of severe constipation.

**Cardiac glycosides:** NSAIDs may 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.

**Cimetidine:** Inhibits the metabolism of opioid analgesics causing increased plasma codeine concentrations.

**Corticosteroids:** An increased risk of gastrointestinal bleeding may occur with corticosteroids.

**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.

**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.

**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.

**Opioid antagonists:** May precipitate withdrawal symptoms.

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

**Medicines 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.

**Ritonavir:** May increase plasma levels of opioid analgesics.

**Tranquillizers, sedatives and hypnotics:** Codeine may potentiate the effects of these medicines.

**Zidovudine:** Concurrent administration with ibuprofen may prolong bleeding time in patients.

## **ADVERSE REACTIONS:**

**Immune system disorders:** Rash, urticaria, pruritus, difficulty breathing, increased sweating, redness of flushed face, angioedema. Exacerbation of asthma and bronchospasm. In patients with existing auto-immune disorders symptoms of aseptic

meningitis such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.

**Gastro-intestinal:** Abdominal pain, peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, ulcerative stomatitis, gastritis, nausea, dyspepsia, diarrhoea, constipation and vomiting.

**Nervous system disorders:** Confusion, malaise, tiredness, vertigo, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental depression, nightmares, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia. Aseptic meningitis has been reported very rarely.

**Haematological:** Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

**Eye Disorders:** Miosis, blurred or double vision.

**Cardiovascular and Cerebrovascular:** Bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia, oedema, hypertension, cardiac failure, arterial thrombotic events (myocardial infarction or stroke).

**Musculoskeletal, connective tissue and bone disorders:** Muscle rigidity.

**Skin:** Skin rash and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen. Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.

**Renal and Urinary Disorders:** Papillary necrosis, which can lead to renal failure. Ureteral spasm, anti-diuretic effect, urinary retention, acute renal failure.

**Reproductive system and Breast Disorders:** Decrease in libido and potency.

**Other:** Hepatic dysfunction, headache, dizziness, hearing disturbance.

**CNS:** Cough suppression, respiratory depression, dizziness and drowsiness.

**Withdrawal effects:** Abrupt withdrawal of codeine precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, and increase in heart rate, respiratory rate and blood pressure.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regular prolonged use of codeine is known to lead to addiction and tolerance. Prolonged use of a painkiller for headaches 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:*****Ibuprofen**

Symptoms of overdose with ibuprofen include nausea, vomiting, abdominal pain, dizziness, drowsiness, nystagmus, blurred vision, tinnitus and rarely, metabolic acidosis and loss of consciousness.

**Codeine**

Nausea and vomiting are prominent features of codeine overdose. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose.

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+'.

***PHARMACEUTICAL PRECAUTIONS:***

Store below 25°C.

***MEDICINES CLASSIFICATION:***

Pharmacist Only Medicine.

***PACKAGE QUANTITIES:***

Packs of 12, 24 and 30 tablets.

***NAME AND ADDRESS:***

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***DATE OF PREPARATION***

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