NEW ZEALAND DATA SHEET

NUROFEN PLUS

WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, Nurofen Plus should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see *section 4.4 Special Warnings and Precautions for Use*).

Hazardous and harmful use
Nurofen Plus poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see *section 4.4. Special Warnings and Precautions for Use*).

Life threatening respiratory depression
Serious, life-threatening or fatal respiratory depression may occur with the use of Nurofen Plus. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see *section 4.4 Special Warnings and Precautions for Use*).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol
Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking Nurofen Plus.

1. TRADE NAME OF THE MEDICINAL PRODUCT

NUROFEN PLUS
Ibuprofen 200mg
Codeine Phosphate Hemihydrate 12.8mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ibuprofen 200.0 mg and codeine phosphate hemihydrate 12.8 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet, film-coated
Nurofen Plus is a white film coated, biconvex capsule-shaped tablet embossed with the logo 'N+' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For 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, and muscular pain.

4.2 Posology and Method of Administration

Posology:

Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken every 4 to 6 times daily as necessary. The maximum daily dose should not exceed 6 tablets in 24 hours.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician. Excessive use can be harmful. Codeine can cause addiction

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults, the elderly and children over 12 years;
Initial dose, two tablets taken with fluid, then one to two tablets every 4 to 6 hours as necessary. Maximum 6 tablets in a 24 hour period

Children aged less than 12 years:

Ibuprofen + Codeine combination solid dose strength products should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 & 4.4).

Elderly:

No special dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case dosage should be assessed individually. NSAIDs should not be used continuously over prolonged periods in the elderly for the management of arthroses without careful supervision.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the ibuprofen, codeine or other opioid analgesics or any of the excipients listed in section 6.1.

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

Severe liver or kidney failure (glomerular filtration rate below 30 mL/min)(see section 4.4).

Severe heart failure (NYHA Class IV).

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

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

Respiratory depression.

Chronic constipation.

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.

3rd trimester of pregnancy (See section 4.6 Pregnancy and Lactation).

Concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment (see section 4.5).

Use of codeine containing products is contraindicated in women during breastfeeding (see section 4.6).

In all children and adolescents aged less than 18 years who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

In all children and adolescents aged less than 18 years for the symptomatic treatment of cough and/or cold due to an increased risk of developing serious and life-threatening adverse reactions.

In all children and adolescents aged less than 18 years in who respiratory function might be compromised.

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

4.4. Special Warnings and Special Precautions for Use

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2, and gastrointestinal and cardiovascular risks below).

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Gastrointestinal effects: 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 section 4.8 – undesirable effects).

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

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 section 4.5).

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

Nurofen Plus tablets should be used with caution in patients with gastrointestinal disease. In patients receiving anti-coagulant therapy, prothrombin time should be monitored daily for the first few days of combined treatment.

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 and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/day) 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. ≤ 1200mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Nurofen Plus should be used with caution in patients with raised intracranial pressure or head injury.

Respiratory: Bronchospasm may be precipitated in patients suffering from or with a history of bronchial asthma or allergic disease. The possibility of cross-sensitivity with aspirin and other non-steroidal anti-inflammatory agents should be considered. If symptoms persist, consult your doctor.

Children with compromised respiratory function
Codeine is not recommended for use in children aged less than 18 years 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 NSAIDs: The use of Nurofen Plus with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease: There is an increased risk of aseptic meningitis in patients with systemic lupus erythematoses and mixed connective tissue disease using the active ingredients in this product (see section 4.8).

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 anti-coagulation therapy.

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

Hepatic: Hepatic dysfunction (see section 4.3 and 4.8).

Severe Skin Reactions:
Dermatological effects: 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 4.8). 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. Acute generalised

exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Nurofen Plus should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections: Nurofen Plus can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Nurofen Plus is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Impaired female fertility: There is some 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.

Do not take concurrently with any other codeine containing compounds.

Care is advised in the administration of codeine to patients with hypotension, asthma, decreased respiratory reserve, acute respiratory depression, obstructive airways disease, prostatic hyperplasia hypothyroidism, adrenocortical insufficiency, shock, head injuries, conditions in which intracranial pressure is raised, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, paralytic ileus, gallstones, myasthenia gravis, and a history of peptic ulcer or convulsions and also in patients with a history of drug abuse and in acute alcoholism.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Codeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to the respiratory depressant effects.

Codeine is a narcotic analgesic. No more than the stated dose of this medicine should be taken. Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. It is important to consult a doctor if a patient experiences the need to use this product all the time.

If you are pregnant or are being prescribed medicines, seek the advice of a doctor before taking this product (see section 4.3).

CYP2D6 metabolism: Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly, resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation, and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1 to 2%

Post-operative use in children: There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid 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.

Keep out of the sight and reach of children.

Hazardous and harmful use
Nurofen Plus contains the opioid codeine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Nurofen Plus at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed Nurofen Plus.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.
Patients should be advised not to share Nurofen Plus with anyone else.

Respiratory depression
Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Nurofen Plus but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g.

chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see *section 4.2 Dose and method of administration*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see *section 4.3 Contraindications*).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see *section 4.2 Dose and method of administration*).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol
Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Nurofen Plus with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe Nurofen Plus concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking Nurofen Plus.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)
Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.
The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see *Hazardous and harmful use, above*). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient

before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see *Ceasing Opioids*).

Tolerance, dependence and withdrawal
Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.
Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate. When discontinuing Nurofen Plus in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids and section 4.2 Dose and Method of Administration*).

Accidental ingestion/exposure
Accidental ingestion or exposure of Nurofen Plus, especially by children, can result in a fatal overdose of [opioid]. Patients and their caregivers should be given information on safe storage and disposal of unused Nurofen Plus (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal*).

Hyperalgesia
Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids
Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see *section 4.2 Dose and Method of Administration*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

4.5 Interactions with other medicinal products and other forms of Interactions

If you are elderly or particularly if you are receiving regular treatment from your doctor, consult your doctor before taking this medicine.

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

Ibuprofen (like other NSAIDs) should not be used in combination with:

- **Acetylsalicylic acid** (aspirin): unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions especially in the gastrointestinal tract (see section 4.4). Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

  Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding the extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1)

- **Other NSAIDs including cyclooxygenase-2 selective-inhibitors:** Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Nurofen Plus should be used with caution in combination with:

- **Anti-coagulants:** NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)

- **Antihypertensives (ACE inhibitors and angiotensin II antagonists) and diuretics:** NSAIDs may diminish the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a cyclooxygenase-2 selective inhibitors concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs. The hypotensive actions of diuretics and anti-hypertensive agents may be potentiated when used concurrently with opioid analgesics.

- **Corticosteroids:** increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

- **Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):** increased risk of gastrointestinal bleeding (see section 4.4)

- **Cardiac glycosides**: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

- **Lithium:** there is evidence for potential increases in plasma levels of lithium.

- **Methotrexate:** there is evidence for potential increases in plasma levels of methotrexate.

- **Ciclosporin:** Increased risk of nephrotoxicity.

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

- **Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

- **Zidovudine:** Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiles receiving concurrent treatment with zidovudine and ibuprofen.

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

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

- **Monoamine oxidase inhibitors:** 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 (see section 4.3).

- **Moclobemide:** risk of hypertensive crisis.

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

- **Central Nervous System Depressants:** The depressant effects of codeine are enhanced by depressants of the central nervous system such as other opioids, alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants or antipsychotics and phenothiazines.

- **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.

- **Abiraterone:** Abiraterone might reduce analgesic effect.

- **Antimuscarinics:** Concomitant use of antimuscarinics or medications with muscarinic action, e.g., atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

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

- **Quinidine:** Quinidine can inhibit the analgesic effect of codeine.

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

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

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

- **Naxolone:** Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

- **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.

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy:
Nurofen Plus is contraindicated in 3rd trimester of pregnancy.

Nurofen Plus should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.

Data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy.

Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Nurofen Plus if oligohydramnios occurs.

NSAID use during the 3rd trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the 3rd trimester of pregnancy is therefore contraindicated (see section 4.3 Contraindications).

Breast-feeding:
This product should not be used during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to 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.

Fertility:
See section 4.4 regarding female fertility.

4.7 Effects on ability to Drive and Use Machines

Patients may become dizzy and sedated with Nurofen Plus. Rare side effects may include convulsions, hallucinations, blurred or double vision and orthostatic hypotension (see section 4.8). 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.

4.8 Undesirable Effects

The list of the following adverse effects relates to those experienced with Ibuprofen and Codeine at OTC doses (maximum 1200mg ibuprofen per day), in short-term use. In the treatment of mild to moderate pain and fever. In the treatment of other indications or under long-term treatment, additional adverse effects may occur.

Adverse events which have been associated with Ibuprofen and Codeine are given below tabulated by System Organ Class (SOC) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1]
Immune system disorders	Uncommon	Hypersensitivity reactions with urticaria and pruritus[2]
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock)[2]
Metabolism and Nutrition Disorders	Not known	Decreased appetite
Psychiatric Disorders	Not known	Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[3]
	Not known	Dizziness, drowsiness, convulsion, intracranial pressure increased, dyskinesia
Eye Disorders	Very rare	Vision blurred
	Not known	Diplopia
Ear and Labyrinth disorders	Not known	Vertigo
Cardiac Disorders	Very rare	Cardiac failure and oedema[4].
	Not known	Bradycardia, palpitations
Vascular Disorders	Very rare	Hypertension[4]
	Not known	Orthostatic hypotension
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea[2] Respiratory depression, cough suppression

Gastro-intestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia. Exacerbation of colitis and Crohn's disease, gastritis[5,6]
	Rare	Diarrhoea, flatulence, constipation and vomiting.
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis[7]. Mouth ulceration
	Not known	Dry mouth
Hepatobiliary Disorders	Very rare	Liver disorder[8]
	Not known	Biliary colic
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash[2]
	Very rare	Severe forms of skin reactions such as erythema multiforme can occur. Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrosis[2]
	Not known	Flushing. Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reactions
Musculoskeletal and Connective Tissue Disorders	Not known	Muscle rigidity
Renal and Urinary Disorders	Very rare	Acute renal failure[9]
	Not known	Ureteric colic, dysuria[10]
General and Administration Site Conditions	Not known	Hypothermia, hyperhidrosis, irritability, fatigue, malaise
Investigations	Very rare	Haemoglobin decreased, urea renal clearance decreased

Description of Selected Adverse Reactions

[1] Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis.
First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding, and bruising.

[2]Hypersensitivity reactions: These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity, including asthma, aggravated asthma, bronchospasm, and dyspnoea, or (c) various skin reactions, including pruritius, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome 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). 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).

[4]Clinical studies suggest that use of Ibuprofen, particularly at a high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

[5]The adverse events observed most often are gastrointestinal in nature.

[6]See Section 4.4.

[7]Sometimes fatal.

[8]Especially in long-term treatment.

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

[10]Increased frequency, decrease in amount.

Post-marketing experience in pregnancy
Oligohydramnios, neonatal renal impairment (see section 4.6)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

In children, ingestion of more than 400 mg/kg ibuprofen may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours. Ingestion of more than 350mg codeine or for a child, more than 5mg codeine per kg of bodyweight, should be considered potentially harmful. Fatalities due to codeine overdose have been reported with intakes above 500mg. Due to the relative concentrations of each active ingredient in the product and their respective toxicity thresholds, the toxic effects of codeine in overdose would be expected to occur before those of ibuprofen.

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastro-intestinal irritation or bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as dizziness, drowsiness, occasionally excitation and disorientation, respiratory depression, excitability, convulsions, loss of consciousness, or coma. Co-ingestion of other sedative agents, including alcohol, may exacerbate effects on the central nervous system. Occasionally patients develop convulsions. The pupils may be pin point in size. Hypotension and tachycardia are possible but unlikely. In serious poisoning, metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount, including more than 350mg codeine or for a child, more than 5mg codeine per kg of bodyweight. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodiliators for asthma.

If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken. Any imbalance in electrolyte levels should be considered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Ibuprofen combinations; **ATC Code:** M01 AE51
Ibuprofen is an NSAID which acts peripherally, inhibiting prostaglandin synthesis and the action of chemical mediators of pain. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation. Codeine is a narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be due largely to its biotransformation to morphine.

The combination of a well tolerated peripheral analgesic with a centrally acting analgesic provides optimum pain relief with a lower potential for producing side effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

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

5.2 Pharmacokinetic Properties

The combination of the two drugs is appropriate from a pharmacokinetic viewpoint; the tablet exhibits normal release characteristics for both active substances.

Ibuprofen is rapidly absorbed from the gastrointestinal tract following administration and is rapidly distributed throughout the whole body. It is extensively bound to plasma proteins and diffused into the synovial fluid. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after one to two hours. These times may vary with different dosage forms.

The half-life of ibuprofen is about two hours.

Codeine phosphate is well absorbed after oral administration, producing peak plasma concentrations in about one hour. The plasma half-life is approximately three hours, excretion being mainly in the urine.

5.3 Preclinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet Core:
Microcrystalline cellulose
Sodium starch glycollate (Type A)
Hypromellose
Pregelatinised maize starch

Film coating:
Hypromellose
Talc
Opaspray white M-1-7111B
(containing Hypromellose and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

Do not store above 25°C.

6.5 Nature and Contents of Containers

Blister packs (PVC/PVDC/aluminium foil) containing 12, 24 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Reckitt Benckiser (New Zealand) Limited
Private Bag 93523
Takapuna
Auckland 0740
New Zealand

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 31 January 2005

Date of last renewal: 12 October 2020

10. DATE OF REVISION OF THE TEXT

9 September 2022 –
Section 4.4 – Revision of Severe Skin Reactions: Dermatological Effects
Section 4.5 – Addition of serotonergic drugs caution
Section 4.6 – Addition of required contraindication for 3rd trimester of pregnancy
Section 4.8 – Addition of required statement regarding post-marketing experience in pregnancy: Oligohydramnios, neonatal renal impairment