

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ibucode Plus, film coated tablets, 200 mg/12.8 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 200 mg of ibuprofen and 12.8 mg codeine phosphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white caplet-shaped, film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

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 aged less than 12 years:

Ibucode Plus is not indicated for use in children under 12 years of age.

Special populations

Elderly

No specific dosage recommendations are required unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

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.

4.3 Contraindications

Ibucode Plus is contraindicated in the following conditions:

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

Patients who have previously shown hypersensitivity reactions (eg, asthma, rhinitis, angioedema, bronchospasm 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 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).

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

Heart or renal problems.

Severe hepatic failure, severe renal failure (glomerular filtration below 30 mL/min) or severe heart failure.

During the last trimester of pregnancy. (See Section 4.6 Fertility, pregnancy and lactation)

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.

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

In all paediatric patients aged less than 18 years who undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to increased risk of developing serious and life-threatening adverse reactions. (see section 4.4 Special warnings and precautions for use).

In adolescents aged less than 18 years in whom respiratory function might be compromised (see section 4.4 Special warnings and precautions for use).

In children aged less than 18 years for the symptomatic treatment of cough and/or cold (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Use with CNS depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Ibucode Plus with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5 Interactions with other medicines and other forms of interaction).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Ibucode Plus is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose

and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5 Interactions with other medicines and other forms of interaction).

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 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. ≤ 1200 mg daily) is associated with an increased risk of myocardial infarction.

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, smoking).

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

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.

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 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.

Care is advised in the administration of Ibucode 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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see Section 4.5 Interactions with other medicines and other forms of interactions).

When gastrointestinal bleeding or ulceration occurs in patients taking Ibucode 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. The possibility of cross-sensitivity with aspirin and other non-steroidal anti-inflammatory agents should be considered.

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

Ibucode 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 Section 4.3 Contraindications).

Aseptic Meningitis

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

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. 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. Ibucode Plus should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

CYP2D6 metabolism

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

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

Population	Prevalence
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2.0%
Caucasian	3.6% to 6.5%

Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children

There have been reports in the published literature that 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 Section 4.3 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 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 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. Ibucode Plus should therefore be administered with caution in such situations.

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

Ibucode Plus should be administered with caution in those 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 (eg. 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.

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.

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

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

4.5 Interaction with other medicines and other forms of interaction

Ibucode 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.

Ibucode 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. IBUCODE PLUS should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

Antiperistaltic and antidiarrhoeals: Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Abiraterone: Abiraterone may reduce analgesic effect.

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 Section 4.4 Special warnings and precautions for use).

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 (including benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol).

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4 Special warnings and precautions for use).

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.

Drugs that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents: Can interfere with the metabolism of codeine to morphine, reducing the 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 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Moclobemide: Risk of hypertensive crisis.

Monoamine oxidase inhibitors (MAOIs): Concurrent administration or use within 14 days of ceasing monoamine oxidase inhibitors may enhance the potential respiratory depressant effects of codeine. CNS depression or excitation may occur if codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them.

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

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

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

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

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

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

Quinidine: Quinidine can inhibit the analgesic effect of codeine.

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

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.

4.6 Fertility, pregnancy and lactation

Fertility

There is limited evidence that drugs which inhibit cyclooxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Use in Pregnancy

Category C: Inhibition of prostaglandin synthesis by ibuprofen may adversely affect pregnancy and/or the embryo/foetal development. Some data from epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. During the first and second trimester of pregnancy, this product should not be given unless clearly necessary, and is contraindicated in the third trimester.

If Ibucode Plus is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible.

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

Ibucode Plus should not be taken during breastfeeding.

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 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 metabolizer 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.

4.7 Effects on ability to drive and use machines

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

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 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.

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, including 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, 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.
Gastrointestinal disorders	Uncommon	Abdominal pain, nausea and dyspepsia. Exacerbation of colitis and Crohn's disease, gastritis ^{5,6}
	Rare	Diarrhoea, flatulence, constipation, 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	Bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis ²
	Not known	Flushing, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
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 administrative site conditions	Not known	Hypothermia, hyperhidrosis, irritability, fatigue, malaise
Investigation	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, 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) various skin reactions, including pruritus, 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, mixed connective tissue disease).

⁴ Clinical studies 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.

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.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (<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 bronchodilators 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: Opioids in combination with non-opioid analgesics, ATC code: N02AJ08

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

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, croscarmellose sodium, microcrystalline cellulose, starch and opadry white.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PVdC/Aluminium foil blister strips.

Packs of 12, 20, 24 and 30 tablets.

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Pharmacist Only Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

15 October 2010

10. DATE OF REVISION OF THE TEXT

2 May 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Dosage recommendations for elderly patients added.
4.3	Additional contraindications for paediatric patients. Age restrictions specified for all paediatric contraindications.
4.4	Age restriction added for paediatric patients with compromised respiratory function.
4.5	Interaction with abiraterone added.
4.4, 4.8, 4.9	Updated safety information.
5.1, 5.2	General update.