AUSTRALIAN PRODUCT INFORMATION

BRUFEN® PLUS 200/12.8

Ibuprofen 200 mg/codeine phosphate hemihydrate 12.8 mg tablet

WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, BRUFEN PLUS 200/12.8 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
BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8. 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 BRUFEN PLUS 200/12.8.

1 NAME OF THE MEDICINE

ibuprofen and codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BRUFEN PLUS 200/12.8 tablet contains 200 mg of ibuprofen and 12.8 mg of codeine phosphate hemihydrate as the active ingredients.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

BRUFEN PLUS 200/12.8: white to off-white capsule-shaped, biconvex, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the temporary relief of acute moderate pain and inflammation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Adults and Children 12 Years and Over

Initial dose two tablets taken with fluid, then one or two tablets every 4 hours when necessary. Maximum dose is 6 tablets in a 24-hour period.

BRUFEN PLUS 200/12.8 should not be used for more than three days at a time unless on medical advice, in which case the patient should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

BRUFEN PLUS 200/12.8 is contraindicated for use in patients who are:

- younger than 12 years
- aged between 12 – 18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea (see **Section 4.3 CONTRAINDICATIONS** and **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – **PAEDIATRIC USE**).

Pregnancy

See Section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

4.3 CONTRAINDICATIONS

- Severe respiratory disease, acute respiratory disease and respiratory depression.
- Known hypersensitivity to ibuprofen, codeine or other opioid analgesics, or any of the excipients
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, bronchospasm, urticaria or allergic-type reactions) in response to ibuprofen with codeine, acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatories (NSAIDs)
- Severe asthma, chronic constipation and active alcoholism
- Active, or a history of ulcerative colitis, Crohn's disease, recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding). As with other NSAID agents, ibuprofen should not be used in active gastrointestinal bleeding or in the presence of peptic ulceration
- Diarrhoea caused by pseudomembranous colitis or poisoning (until the cause organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).
- Use with other concomitant NSAIDs (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**), including cyclo-oxygenase-2 specific inhibitors – increased risk of adverse reactions
- Severe heart failure (NYHA Class IV) and severe renal failure (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
- Severe hepatic impairment (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
- Third 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
- In patients who are CYP2D6 ultra rapid metabolisers (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – **CYP2D6 METABOLISM**)
- In patients younger than 12 years (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – **PAEDIATRIC USE**)
- In patients aged between 12 – 18 years in whom respiratory function might be compromised, including post tonsillectomy, and/or adenoidectomy for obstructive sleep apnoea due to an increased risk of developing serious life-threatening adverse reactions (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – **PAEDIATRIC USE**)

- Use of codeine containing products is contraindicated in women during breastfeeding (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION** – **USE IN LACTATION**)
- Treatment of perioperative pain in setting of coronary artery bypass surgery (CABG)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

BRUFEN PLUS 200/12.8 should be administered with caution and at lowest effective dose in patients:

- with decreased respiratory reserve, e.g. asthma or COPD
- with asthma, especially those patients who have not taken an NSAID (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – **Respiratory and also Respiratory Depression**)
- who are taking other respiratory depressants or sedatives (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol**)
- with hepatic, renal or cardiac impairment (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CARDIAC, RENAL AND HEPATIC IMPAIRMENT**).
- with hypotension
- with previous history of gastrointestinal haemorrhage or ulcers (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - GASTROINTESTINAL**)
- who have had recent gastrointestinal surgery, paralytic ileus, as codeine may reduce gastrointestinal motility.
- with hypothyroidism
- with a tendency for convulsions
- with prostatic hypertrophy; codeine may cause urinary retention
- with raised intracranial pressure or head injury
- who are pregnant (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION – USE IN PREGNANCY, USE IN LACTATION** and **Section 4.3 CONTRAINDICATIONS**)
- who are over the age of 65 (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – USE IN ELDERLY**)

Hazardous and harmful use

BRUFEN PLUS 200/12.8 contains the opioid codeine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8.

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 BRUFEN PLUS 200/12.8 with anyone else.

In view of the potential development of physical dependency to codeine, long-term use is not recommended.

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 BRUFEN PLUS 200/12.8 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, in patients with renal and hepatic impairment (see Use in hepatic impairment and Use in renal impairment) 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), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

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 BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8.

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 BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8, especially by children, can result in a fatal overdose of codeine. Patients and their caregivers should be given information on safe storage and disposal of unused BRUFEN PLUS 200/12.8 (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal).

Central sleep apnoea

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.

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.

Skin and subcutaneous tissue disorders

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, Drug Reaction with Eosinophilia with Systemic Symptoms and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. BRUFEN PLUS 200/12.8 use should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Severe skin reactions

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. The acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of BRUFEN PLUS 200/12.8 should be discontinued and appropriate measures taken if needed.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Masking of symptoms of underlying infections

BRUFEN PLUS 200/12.8 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 BRUFEN PLUS 200/12.8 is administered for fever or pain relief in relation to infection, monitoring infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Gastrointestinal

NSAIDS should be given with care to patients with a history of peptic ulceration and gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see **Section 4.3 CONTRAINDICATIONS** and **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see **Section 4.3 CONTRAINDICATIONS**) and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents should be considered for these patients, as well as patients requiring concomitant low dose acetylsalicylic acid/aspirin, or for other drugs likely to increase gastrointestinal risk (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

The concomitant administration of ibuprofen and other NSAIDs, including cyclooxygenase-2 (COX-2) selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Patients with a history of GI toxicity, particularly the elderly, patients with a history of gastrointestinal bleeding or perforation or peptic ulcer haemorrhage related to previous NSAID therapy should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Care is advised in the administration of BRUFEN PLUS 200/12.8 to patients with obstructive bowel disorders, recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of peptic ulcer or convulsions.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).
When GI bleeding or ulceration occurs in patients receiving BRUFEN PLUS 200/12.8, the treatment should be withdrawn.
Codeine should be used with caution in patients with biliary tract disease, including acute pancreatitis, as codeine may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.
Chronic use of opioids, including codeine, can cause or aggravate chronic constipation since, although a level of tolerance to the effects of opiates on bowel movements is developed, patients who take opiates to treat a chronic condition continue to suffer from constipation.

Respiratory

Bronchospasm may be precipitated in patients suffering from, or with a history of bronchial asthma, chronic rhinitis or allergic disease.

SLE and Mixed Connective Tissue Disease

Use of ibuprofen in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease can increase the risk of aseptic meningitis (see below).

Aseptic Meningitis

Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Cardiac, Renal and Hepatic Impairment

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The habitual concomitant intake of similar painkillers further increases this risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see **Section 4.3 CONTRAINDICATIONS**). See below for further information on cardiac, renal and hepatic impairment.

Use in Hepatic Impairment

As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.
BRUFEN PLUS 200/12.8 should be administered with caution in patients with mild to moderate hepatic impairment (see **Section 4.3 CONTRAINDICATIONS** for severe hepatic impairment). Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the steps to take should these signs and/or symptoms occur.
Codeine is metabolised by the liver and should be used with caution in patients with hepatic disease, since increased bioavailability after oral administration or cumulative effects may occur.

Use in Renal Impairment

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.
Caution should be exercised in patients with renal impairment as renal function may deteriorate, especially in dehydrated paediatric patients (see **Section 4.3 CONTRAINDICATIONS** and **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).
As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes.
Opioids and their metabolites are excreted primarily via the kidneys. Because of this there is an increased risk of adverse effects in patients with renal function impairment.

Cardiovascular and Cerebrovascular Effects

Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischemic 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 and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.
BRUFEN PLUS 200/12.8 should be administered with caution in patients with hypertension or fluid retention (see **Section 4.3 CONTRAINDICATIONS**).

Haematological Effects

Ibuprofen with codeine should be given with care to patients receiving anticoagulant therapy and appropriate monitoring should be conducted.

CYP2D6 Metabolism

BRUFEN PLUS 200/12.8 is contraindicated for use in patients who are CYP2D6 ultra-rapid metabolisers.
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. 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. Children are particularly susceptible due to their immature airway anatomy. Deaths have been reported in children with rapid metabolism who were given codeine for analgesia post adenotonsillectomy. Morphine can also be ingested by infants through breast milk, causing risk of respiratory depression in infants of rapid metaboliser mothers who take codeine.
The prevalence of codeine ultra-rapid metabolism by CYP2D6 in children is not known, but it is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1% to 10% in Caucasians. The highest prevalence (16% to 28%) occurs in North African, Ethiopian and Arab populations. See also sections on **4.4 SPECIAL WARNINGS AND PRECAUTION FOR USE – PAEDIATRIC USE** and **4.6 FERTILITY, PREGNANCY AND LACTATION – USE IN LACTATION**. Estimates of prevalence of ultra- rapid metabolisers in different populations are summarised below:

Table 1.

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%

(See also sections on **4.4 SPECIAL WARNINGS AND PRECAUTION FOR USE – PAEDIATRIC USE** and **4.6 FERTILITY, PREGNANCY AND LACTATION – USE IN 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.
Ibuprofen should not be taken by adults over the age of 65 without careful consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment.
The elderly are also more likely to have age related renal impairment and may be more susceptible to the respiratory depressant effects of codeine.
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 **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – GASTROINTESTINAL**).

Paediatric Use

BRUFEN PLUS 200/12.8 is contraindicated for use in children:

- younger than 12 years
- aged between 12 – 18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-metabolisers of codeine due to CYP2D6 polymorphism. See also **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 METABOLISM**

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 contraindicated 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.

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
In patients with renal impairment, renal function should be monitored since it may deteriorate following the use of any NSAID.
As with other NSAIDs, excessive or prolonged use of ibuprofen may increase the risk of heart attack, stroke or liver damage.
As with other NSAIDS, ibuprofen may mask the usual signs of infection.
The concomitant use of alcohol should be avoided.
Codeine may also obscure the diagnosis or the course of gastrointestinal diseases. BRUFEN PLUS 200/12.8 should therefore be administered with caution in such situations. Care is advised in the administration of BRUFEN PLUS 200/12.8 to patients with adrenocortical insufficiency and also in patients with a history of drug abuse.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

BRUFEN PLUS 200/12.8 should be avoided in combination with:
Alcohol: can increase the depressive effect of codeine.
Aspirin: as with other products containing NSAIDs, concomitant administration of ibuprofen and acetylsalicylic acid/aspirin is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. 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/ aspirin cannot be excluded. 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 due to the potential for additive effects, as this may increase the risk of adverse effects (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

BRUFEN PLUS 200/12.8 should be used with caution in combination with:
Abiraterone: Abiraterone might reduce analgesic effect of codeine by CYP2D6 inhibition.
Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.
Anticholinergics: concurrent use of codeine, and anticholinergics or other medications with anticholinergic activity may increase the risk of severe constipation and/or urinary retention, which may lead to paralytic ileus.
Anticoagulants: ibuprofen interferes with the stability of INR. NSAIDs may enhance the effects of anticoagulants, such as warfarin. Concurrent use of NSAIDs and warfarin has been associated with severe bleeding and 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. BRUFEN PLUS 200/12.8 should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.
Antidiarrhoeal and anti-peristaltic agents: concurrent use of codeine with antidiarrhoeal and anti-peristaltic agents such as loperamide, pectin and kaolin may increase the risk of severe constipation.
Antimuscarinics: concomitant use of antimuscarinics or medications with muscarinic action, e.g. atropine and some antidepressants, may result in increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.
ACE inhibitors, diuretics and other antihypertensives: ibuprofen, like other NSAIDs may reduce the antihypertensive effect of ACE Inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics, with possible loss of blood pressure control, and may cause natriuresis and hyperkalaemia in patients under these treatments.
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, e.g. clopidogrel and ticlopidine, and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding with NSAIDS (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.
Central nervous system depressants: concomitant use of codeine with central nervous system depressants (e.g. barbiturates, chloral hydrate, sedatives, alcohol and centrally acting muscle relaxants) can cause additive CNS depression.
Colestyramine: the concomitant administration of ibuprofen and colestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.
Ciclosporin: an increased risk of nephrotoxicity with NSAIDs.
Cimetidine: cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Corticosteroids: an increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
CYP2C9 inhibitors: concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.
Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, phenothiazines and antipsychotic agents: can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.
Herbal extracts: ginkgo biloba may potentiate the risk of bleeding with NSAIDs.
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 and caution should be used if low doses of methotrexate are administered concomitantly with ibuprofen.
Mexiletine: codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.
Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone, due to the antiprostaglandin properties of NSAIDs.
Moclobemide: risk of hypertensive crisis.
Monoamine Oxidase Inhibitors (MAOIs): concurrent administration or use within 14 days of ceasing MAOIs 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, phenytoin and antidiabetic medicines: 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.
Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.
Sedative medicines such as benzodiazepines or other CNS depressants: the concomitant use of opioid containing products (e.g. codeine) with sedative medicines such as benzodiazepines, other opioid analgesics, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, including alcohol increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
Serotonergic drugs: Serotonin syndrome has been reported during concomitant use of serotonergic drugs including triptans, selective serotonin-reuptake inhibitors (SSRIs), selective serotonin-and norepinephrine-reuptake inhibitors (SNRIs), and tricyclic antidepressants, with opioids at recommended dosages.
Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Tranquillizers, sedatives and hypnotics: codeine may potentiate the effects of these preparations.

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. Concurrent administration with ibuprofen may prolong bleeding time in patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 on withdrawal of treatment.

Use in Pregnancy

Pregnancy Category: C
Inhibition of prostaglandin synthesis by ibuprofen may adversely affect pregnancy and/or the embryo/foetal development. During the first and second trimester of pregnancy, this product should not be given unless clearly necessary, and is contraindicated in the third trimester.
During the third trimester, all prostaglandin synthesis inhibitors may expose the foetus to cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction, which may progress to renal failure with oligohydramnios (see Oligohydramnios and Neonatal Renal Impairment). 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.
Consequently, ibuprofen with codeine is contraindicated during the third trimester of pregnancy.
Administration of ibuprofen with codeine is not recommended during labour and delivery. The use of codeine may prolong labour. Administration of codeine during labour may cause respiratory depression in the newborn infant. It is not advisable to use it during labour if the baby is premature.
Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate.
Codeine can cause the newly born to suffer from withdrawal syndrome in case of administration of codeine-containing medications in the days prior to delivery. It is therefore recommended to closely monitor the newly born whose mother took opiates during labour.
BRUFEN PLUS 200/12.8 is contraindicated for use during the third trimester of pregnancy (see **Section 4.3 CONTRAINDICATIONS**).

Oligohydramnios and Neonatal Renal Impairment

Use of NSAIDs from about 20 weeks gestation may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.
These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.
Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

Contraindicated in the third trimester of pregnancy (see **Section 4.3 CONTRAINDICATIONS**).

Use in Lactation

BRUFEN PLUS 200/12.8 is contraindicated during breastfeeding (see also **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - CYP2D6 METABOLISM**) due to risk of respiratory depression in the infant.
Ibuprofen appears in breast milk in very low concentrations. Analgesic doses excreted in breast milk are generally low. However, infants of breast-feeding mothers taking codeine may have increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine.

Codeine is excreted into human breast milk. Codeine is partially metabolised by cytochrome P450 2D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breastfed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 METABOLISM**).
Therefore, BRUFEN PLUS 200/12.8 is contraindicated for use during breastfeeding. However, in circumstances where a breastfeeding mother requires codeine therapy, breastfeeding should be suspended, and alternative arrangements should be made for feeding the infant for any period during codeine treatment.
Breast feeding mothers should be told how to recognise signs of high morphine levels in themselves and their babies. For example, in a mother, symptoms include extreme sleepiness, and trouble caring for the baby. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Medical advice should be sought immediately.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs.
Codeine may cause drowsiness. Sedation with altered reaction time due to codeine may occur.
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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal Disorders
The most commonly observed adverse events are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding which is dependent on the dosage range and duration of treatment.

Infections and Infestations
Exacerbation of skin infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of ibuprofen the patient should immediately seek medical attention.

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.

The list of the following adverse events relates to those experienced with ibuprofen and codeine (maximum of 1200mg ibuprofen per day), for 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.

The frequencies of adverse effects are defined as follows:
Very common: ≥ 1/10
Common: ≥ 1/100, < 1/10
Uncommon: ≥ 1/1,000, < 1/100
Rare: ≥ 1/10,000, < 1/1,000
Very Rare: < 1/10,000, including isolated reports
Not known: cannot be estimated from the available data.

Within each frequency grouping, adverse events are presented in order of decreased seriousness.

Table 2.

System Organ Class	Frequency	Adverse Events
Infections and infestations	Uncommon	Rhinitis
	Rare	Aseptic meningitis[4]
Blood and Lymphatic System Disorders	Rare	Haematopoietic disorders[1]
	Very rare	Alveolitis, pulmonary eosinophilia, pancreatitis, haemoglobin decreased, platelet aggregation[2]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus[3]
	Rare	Severe hypersensitivity reactions, including swelling of the face, swollen tongue and laryngeal oedema, dyspnoea, apnoea and tachycardia, (anaphylaxis, angioedema or severe shock)[3]
Metabolism and Nutrition Disorders	Not known	Decreased appetite
Psychiatric Disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
	Not known	Hallucination, dependence, mood altered, restlessness, nightmares, irritability, euphoria, dysphoria
Nervous System Disorders	Common	Drowsiness, headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis
	Very rare	Nervousness, disturbance in attention, affect lability, convulsions
	Not known	Intracranial pressure increased, dyskinesia, miosis
Eye Disorders	Uncommon	Visual impairment[5]
	Rare	Dry eye, toxic optic neuropathy
	Very Rare	Vision blurred, amblyopia
	Not known	Diplopia
Ear and Labyrinth Disorders	Uncommon	Hearing impaired, tinnitus, vertigo
Cardiac Disorders	Rare	Palpitations[6]
	Very Rare	Cardiac failure, myocardial infarction (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
	Not known	Oedema, bradycardia
Vascular Disorders	Rare	Cerebrovascular accident[6], hypotension, cardiac failure congestive[7]
	Very Rare	Hypertension
	Not known	Orthostatic hypotension[6]
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Asthma, bronchospasm, dyspnoea[3]
	Not known	Respiratory depression, cough suppression
Gastrointestinal Disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, hematemesis[8], gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Rare	Dry mouth, gingival ulceration
	Very rare	Pancreatitis, peptic ulcer, exacerbation of ulcerative colitis and Crohn's disease[9]
Hepatobiliary Disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Very rare	Liver disorder[10], hepatic failure
	Not known	Biliary colic
Skin and Subcutaneous Tissue Disorders	Common	Skin rash[3]
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction
	Rare	Skin exfoliation, alopecia, dermatitis exfoliative, rash maculopapular, hyperhidrosis

	Very rare	Severe forms of skin reactions (e.g. erythema multiforme, bullous reactions including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis[3]
	Not known	Flushing, DRESS (Drug reaction with eosinophilia and systemic symptoms), AGEP (Acute Generalized Exanthematous Pustulosis)
Musculoskeletal and Connective Tissue Disorders	Not known	Muscle rigidity
Renal and Urinary Disorders	Uncommon	Nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure[11]
	Not known	Renal colic, dysuria[12]
Pregnancy, puerperium and perinatal conditions	Not known	Oligohydramnios, neonatal renal impairment
General Disorders and Administration Site Conditions	Common	Fatigue
	Rare	Oedema
	Not known	Hypothermia, malaise
Investigations	Very rare	Haemoglobin decreased

Description of Selected Adverse Reactions

[1] Examples include anaemia, neutropenia, aplastic anaemia, haemolytic anaemia, eosinophilia, reduction of haemoglobin and haematocrit leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

[2] Reversible.

[3] Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:

a) non-specific allergic reactions and anaphylaxis
b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme). Severe shock syndrome may be characterised by abdominal pain, fever, shivering, nausea and vomiting. Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions.

[4] The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSID related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff, neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus and mixed connective tissue disease).

[5] Includes changes in visual colour perception.

[6] Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke), (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

[7] In patients with compromised cardiac function.

[8] Sometimes fatal, particularly in the elderly.

[9] See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

[10] Especially in long term treatment, including hepatotoxicity, hepatitis, jaundice, alterations of hepatic function tests, pancreatitis, duodenitis, oesophagitis, hepatorenal syndrome, hepatic necrosis, hepatic insufficiency.

[11] Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis. Ibuprofen may cause cystitis and haematuria, interstitial nephritis, nephrotic syndrome, oliguria, tubular necrosis, glomerulonephritis, alteration in the renal function test, polyuria, anaphylaxis.

[12] Increased frequency, decrease in amount.

Post-marketing experience:

A causal association for the following adverse effects has not yet been established however they could not be excluded as a possible class-effect:

Pregnancy, puerperium and perinatal conditions: Oligohydramnios, neonatal renal impairment

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Symptoms

Ibuprofen

The most frequently reported symptoms of ibuprofen overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. CNS effects include headache, dizziness, tinnitus, convulsions and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. Symptoms of overdose also include vertigo, blurred vision, tinnitus and rarely, diarrhoea, hypertension, excitation, disorientation, and cyanosis. In cases of significant overdose, renal failure and liver damage are possible. Exacerbation of asthma is possible in asthmatics.

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. Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pinpoint in size. Hypotension and tachycardia are possible.

Treatment

Ibuprofen

There is no specific antidote to ibuprofen. Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. If necessary, serum electrolyte balance should be corrected.

Codeine

In an overdose of codeine, parenteral naloxone may be administered in connection with resuscitation if serious respiratory and/or cardiovascular depression has occurred.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDS). Its mechanism of action is unknown but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition.

Codeine acts centrally on opiate receptors. Its analgesic effect is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one- sixth the analgesic activity of morphine.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ibuprofen
It is well absorbed from the gastrointestinal tract after oral administration with peak serum levels occurring after 1-2 hours.
Codeine
Codeine and its salts are well absorbed from the gastrointestinal tract. Peak plasma-codeine concentrations occur at about one hour after ingestion of codeine phosphate hemihydrate. Analgesic action occurs in 15 to 30 minutes and analgesia is maintained up to 4- 6 hours.

Distribution

Ibuprofen
Apparent volume of distribution is 0.14L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant animals (rabbits & rats). It is not known if ibuprofen enters the cerebrospinal fluid.
Codeine
After ingestion 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

Ibuprofen
90% of ibuprofen is metabolised to inactive compounds in the liver, mainly by glucuronidation, to produce two metabolites - a hydroxylated compound and a carboxylated compound.
Codeine
Codeine is metabolised by O- and N-demethylation in the liver (by CYP2D6 and CYP3A4 respectively) to morphine (about ten percent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. The major metabolic pathway involves glucuronidation of codeine to codeine-6-glucuronide. About 8% of the general Australian population cannot convert codeine to its active metabolite morphine as they are deficient in the CYP2D6 enzyme. These persons are likely to obtain reduced pain relief from codeine.

Excretion

Ibuprofen
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.
Codeine
Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. 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. Excretion is almost complete within 24 hours. The plasma half-life of codeine has been reported to be between 2 and 4 hours after oral administration. Only traces of codeine and its metabolites are found in the faeces.

Protein binding

Ibuprofen
It is highly bound (90-99%) to plasma proteins and consequently, this characteristic of the drug should be considered when prescribing ibuprofen together with other drugs that bind to the same site on human serum albumin.

Half-life

Ibuprofen
The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, pregelatinised maize starch, croscarmellose sodium, colloidal anhydrous silica, and Opadry complete film coating system OY-58900 White (ARTG PI No: 3446).

6.2 INCOMPATIBILITIES

Codeine has been reported to be incompatible with phenobarbital (phenobarbitone) sodium forming a codeine phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide. Acetylation of codeine phosphate hemihydrate by acetylsalicylic acid (aspirin) has occurred in solid dosage forms containing the two drugs, even at low moisture levels.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in PVC/PVDC blisters in the following pack sizes: 10s, 12s, 15s, 20s, 24s and 30s.
Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 298439 - BRUFEN PLUS 200/12.8 Ibuprofen 200 mg and codeine phosphate hemihydrate 12.8 mg tablet blister pack

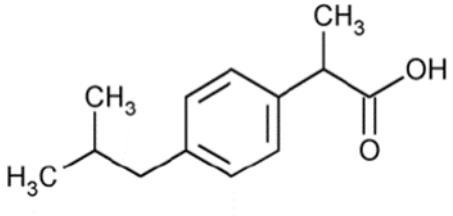
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

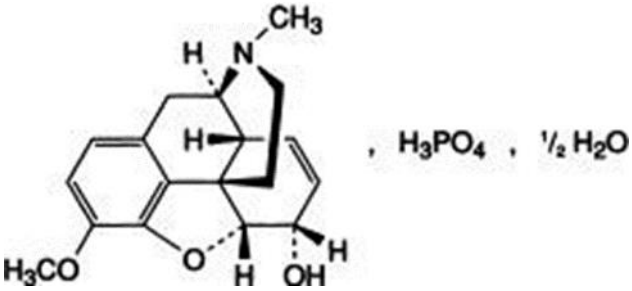
Ibuprofen
It is a white or almost white powder or crystals with a characteristic odour. Practically insoluble in water, soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone; soluble in aqueous solutions of alkali hydroxides and carbonates.



Chemical name: 2-(4-Isobutylphenyl) propionic acid
Molecular Formula: $C_{13}H_{18}O_2$
MW: 206.3

Codeine phosphate hemihydrate

It is a small, colourless, odourless crystal or a white, odourless crystalline powder. Codeine phosphate hemihydrate is soluble in four parts water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.



Chemical name: (5R, 6S)-7, 8-didehydro-4,5-epoxy-3-methoxy-N-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate

Molecular formula: C18H21NO3.H3PO4•½ H2O

MW: 406.4

CAS Number

Ibuprofen 15687-27-1

Codeine phosphate hemihydrate 41444-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

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www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

28/03/2018

10 DATE OF REVISION

30/01/2023

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Addition of central sleep apnoea
4.5	Addition of interaction with serotonergic drugs
All	Minor editorial changes

BRUFEN® PLUS is a Viatris company trade mark

BRUFEN PLUS_pi\Jan23/00