# AUSTRALIAN PRODUCT INFORMATION

## IBUDEINE (IBUPROFEN 200MG, CODEINE PHOSPHATE HEMIHYDRATE 12.8 MG) TABLETS

**WARNINGS**

***Limitations of use***

**Because of the risks associated with the use of opioids, IBUDEINE 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***

**IBUDEINE 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 IBUDEINE. 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 IBUDEINE.**

## 1 NAME OF THE MEDICINE

Ibudeine

Ibuprofen 200 mg, Codeine Phosphate Hemihydrate 12.8 mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ibuprofen 200mg and codeine phosphate hemihydrate 12.8mg.

**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 1of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone; soluble in aqueous solutions of alkali hydroxides and carbonates.

**Codeine:** 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.

Ibudeine tablets do not contain gluten or preservatives.

Excipients of known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

White to off-white capsule-shaped biconvex film-coated tablets with a central breakline on one side and plain on the other, supplied in blister packs.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Ibudeine is used for temporary relief of acute moderate pain and inflammation.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

**Adults and children over 12 years of age:** Initial dose two tablets taken with fluid, then one or two tablets every 4 to 6 hours when necessary. Maximum dose is 6 tablets in a 24-hour period.

Ibudeine is contraindicated 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 also section 4.3 Contraindications, section 4.4 Special warnings and Precautions

for use – Paediatric Use and CYP2D6 Metabolism.)

## 4.3 CONTRAINDICATIONS

- hypersensitivity or idiosyncratic reaction to ibuprofen, codeine or other opioid analgesics, or any other ingredients in the product listed in the Description section above
- hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Severe respiratory disease, acute respiratory disease and respiratory depression (for example, acute asthma, acute exacerbations of chronic obstructive pulmonary disease), especially in the presence of cyanosis and excessive bronchial secretion, since codeine may exacerbate the condition
- active alcoholism
- renal impairment
- heart failure
- patients with severe hepatic impairment
- treatment of perioperative pain in setting of coronary artery bypass surgery (CABG)
- conditions involving an increased tendency of bleeding or active bleeding
- use of ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy)
- breast-feeding (see section 4.6 Fertility, Pregnancy and Lactation - Use in Lactation)
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate
- a history of, or active, gastrointestinal bleeding or perforation, ulcerative colitis, Crohn's disease, gastrointestinal haemorrhage, or peptic ulceration
- chronic constipation
- 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).
- taking other products containing ibuprofen or with other anti-inflammatory medicines (see section 4.5 Interactions with Other Medicines and Other forms of interactions)
- in patients who are:
    - CYP2D6 ultra-rapid metabolisers (see section 4.4 Special warnings and Precautions for use – CYP2D6 metabolism)
    - younger than 12 years (see section 4.4 Special warnings and Precautions for use – Paediatric Use)
    - 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 and life-threatening adverse reactions (see section 4.4 Special warnings and Precautions for use – Paediatric Use)

Refer to section 4.5 Interactions with Other Medicines and Other forms of interactions for additional information.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ibudeine should be administered with caution and at lowest effective dose in patients:

- who have not taken an NSAID before
- who are taking other respiratory depressants or sedatives, including alcohol
- with hepatic impairment (severe hepatic impairment is contraindicated, see section 4.3 Contraindications; also see section 4.4 Special warnings and Precautions for use – Impaired Liver Function)
- with hypotension.

Codeine should be administered with caution and at the lowest effective dose in patients:

- with acute abdominal conditions, since codeine may obscure the diagnosis or the course of gastrointestinal diseases.
- with severe inflammatory bowel disease (risk of toxic megacolon may be increased, especially with repeated dosing).
- who have had recent gastrointestinal tract surgery.
- with CNS depression or decreased respiratory reserve, e.g. emphysema, kyphoscoliosis, hypoxia, hypercapnia, or even severe obesity or cor pulmonale, or chronic obstructive pulmonary disease.
- with hypothyroidism, adrenocortical insufficiency (e.g. Addison's disease), shock, myxoedema, acute alcohol intoxication or delirium tremens, since codeine may exacerbate the symptoms or increase the risk of respiratory and/or CNS depression.
- with a history of convulsive disorders (convulsions may be induced or exacerbated by codeine).
- with prostatic hypertrophy, urethral stricture or recent urinary tract surgery, since codeine may cause urinary retention.
- in elderly or debilitated patients because of the danger of respiratory or cardiac depression (see section 4.4 Special warnings and Precautions for use - Use in the Elderly).

Codeine should be administered with great caution in patients with head injury, brain tumour, or increased intracranial pressure, since codeine may increase the risk of respiratory depression and further elevate intracranial pressure. In addition, codeine can produce side effects such as confusion, miosis and vomiting, which are important signs in following the clinical course of patients with head injuries.

Through concomitant consumption of alcohol, NSAID-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Prolonged use of any painkillers, such as ibuprofen or codeine, may induce headaches, which must not be treated with increased doses of the painkillers, including ibuprofen.

## *Hazardous and harmful use*

Ibudeine contains the opioid [active ingredient] and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Ibudeine 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 Ibudeine.

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 Ibudeine with anyone else.

### *Respiratory depression*

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Ibudeine 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, 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.

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, chronic rhinitis or allergic diseases, since ibuprofen has been reported to cause bronchospasm, urticarial or angioedema in such patients.

### *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 Ibudeine 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 Ibudeine 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 Ibudeine.

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

### *Hyperalgesia*

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

### *Ceasing opioids*

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

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

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

#### *CYP2D6 Metabolism*

Ibudeine 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 to 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 to infants of rapid metaboliser mothers who take codeine.

The prevalence of codeine ultra-rapid metabolism by CYP2D6 in children is not known, but 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%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations.

(See also the sections section 4.4 Special warnings and Precautions for use - Paediatric Use and section 4.6 Fertility, Pregnancy and lactation - Use in Lactation.)

***Cardiovascular (CV) Thrombotic Events***
Clinical studies suggest that use of ibuprofen, particularly at a high dose or increased duration of use, may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. Patients with uncontrolled hypertension, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses should be avoided.

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

To minimize the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

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

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.

***Hypertension***
NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

***Heart Failure***

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention. Ibudeine is contraindicated in patients with heart failure (see section 4.3 Contraindications).

***Gastrointestinal Events***

Ibudeine is contraindicated in patients with a history of, or active, gastrointestinal bleeding or perforation, ulcerative colitis, Crohn's disease, gastrointestinal haemorrhage, or peptic ulceration (see section 4.3 Contraindications).

All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal, gastrointestinal effects such as ulcers, bleeding and perforation, which may increase with dose or duration of use, but can occur at any time without warning.

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).

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, smoking and alcoholism (active alcoholism is contraindicated – see section 4.3 Contraindications). When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about signs and symptoms of serious gastrointestinal toxicity.

Caution should be exercised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or antiplatelet drugs such as aspirin (see section 4.5 Interactions With Other Medicines and other forms of interactions).

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

***Severe Skin Reactions***

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Severe skin infections and soft-tissue complications may occur in patients with a varicella infection. Therefore, it is advisable to avoid the use of ibuprofen in known or suspected cases of varicella.

***Infections and Infestations***
Exacerbation of 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 is therefore recommended to go to a doctor without delay.

***Ophthalmological Effects***
Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

***Combination use of ACE inhibitor or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics***
The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with at risk of renal impairment.

***Aseptic Meningitis***
Aseptic meningitis has been reported only rarely with ibuprofen, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

***Haematological Monitoring***
Blood dyscrasias have been rarely reported with ibuprofen. 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, 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. Ibudeine is contraindicated in patients with conditions involving an increased tendency of bleeding or active bleeding, such as those on anti-coagulation therapy (see section 4.3 Contraindications and section 4.5 Interactions with Other Medicines and other forms of interactions).

***Masking Signs of Infection***
As with other NSAIDs, ibuprofen may mask the usual signs of infection.

**Use in hepatic impairment**: As with other NSAIDs, elevations of one or more liver function tests may occur in some patients.

Physicians and patients should remain alert for hepatotoxicity. Patients should 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. Patients with impaired liver function or a history of liver disease who are on ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued. The use of Ibudeine is contraindicated in patients with severe hepatic impairment.

**Use in renal impairment**: Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children and adolescents.

The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In patients with cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. The long-term concomitant intake of similar analgesics further increases the risk. For patients with hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function.

**Use in the elderly:** 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.

**Paediatric use:** Ibudeine 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-rapid metabolisers of codeine due to CYP2D6 polymorphism.

(See also section 4.4 Special warnings and precautions for use – CYP2D6 Metabolism.)

**Effects on laboratory tests**: Plasma amylase and lipase activity: Codeine may cause increased biliary tract pressure, thus increasing plasma amylase and/or lipase concentrations.

Gastric emptying studies: Gastric emptying is delayed by codeine, so gastric emptying studies will not be valid.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The following interactions have been noted:

- anti-coagulants, including warfarin, due to an enhanced effect of anti-coagulants. Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage. Ibuprofen interferes with the stability of INR (International Normalised Ratio) and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibudeine is contraindicated in patients with conditions involving an increased tendency of bleeding or active bleeding, such as those on anti-coagulation therapy (see section 4.3 Contraindications).
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.
- Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.
- Ibuprofen may decrease renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.
- Ibuprofen, like other NSAIDs, may reduce the anti-hypertensive effect of ACE inhibitors, angiotensin II-receptor antagonists, beta-blockers, and diuretics, with possible loss of blood pressure control, and may cause natriuresis and hyperkalemia in patients under these treatments. The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor agonist), an anti-inflammatory drug (NSAID or COX-2) inhibitor and thiazide diuretic at the same time increases the risk of renal impairment (see section 4.4 Special warnings and precautions for use – use in renal impairment). This includes use in fixed combination medicines containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution. Diuretics can also increase the risk of nephrotoxicity of NSAIDs.
- Ibuprofen reduces methotrexate clearance. Use of high doses of methotrexate

concomitant with NSAIDs should be avoided. At low doses of methotrexate caution should be used if ibuprofen is administered concomitantly.

- NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate, and increase plasma levels of cardiac glycosides. Care should therefore be taken in patients treated with cardiac glycosides.
- Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract.
- Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.
- Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids.
- Cyclosporine or Tacrolimus: increased risk of nephrotoxicity when used with NSAIDs.
- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.
- Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Ibuprofen may prolong bleeding time in patients treated with zidovudine.
- 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.
- Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.
- CNS depressants - concomitant use of codeine with central nervous system depressants (e.g. benzodiazepines, barbiturates, chloral hydrate, hypnotics, sedatives, tranquillisers, other opioid analgesics, gabapentinoids, cannabis, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, centrally acting muscle relaxants and/or other CNS depressants) including alcohol, can cause additive CNS depression and may result in sedation, respiratory depression, coma and death. (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines and other CNS depressants, including alcohol)
- Alcohol: the concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death, because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines and other CNS depressants, including alcohol.)
- Anticholinergics: concurrent use of codeine with anticholinergic agents may increase the risk of severe constipation and/or urinary retention.

- Antihypertensives: hypotensive effects may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.
- Antiperistaltic antidiarrhoeals (e.g. kaolin, pectin and loperamide) - concurrent use with codeine may increase the risk of severe constipation.
- Metoclopramide: codeine may antagonise the effects of metoclopramide on gastrointestinal activity.
- Monoamine oxidase inhibitors (MAOIs) – non-selective MAOIs intensify the effects of opioid drugs, which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment.
- Neuromuscular blocking agents: codeine may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.
- Opioid analgesics: concurrent use of codeine and other opioid receptor antagonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines and other CNS depressants, including alcohol).
- Substances that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine
- Other analgesics: Concomitant use of ibuprofen with other NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, is contraindicated (see Contraindications), because of the potential of increased adverse effects.
- Effects on ability to drive and to use machines: following treatment with ibuprofen, the reaction time of patients may be affected. This should be taken into account where increased vigilance is required, e.g. when driving a car or operating machinery.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

**Use in pregnancy**

**Category C:** Ibuprofen inhibits prostaglandin synthesis, which may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use

of a prostaglandin synthesis inhibitor in pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses and embryo/foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Use of this medicine is contraindicated in the third trimester of pregnancy, including the last few days before the expected birth. Further, there is insufficient experience with the safety of ibuprofen use in humans during pregnancy. Ibudeine should therefore not be used during the first 6 months of pregnancy unless clearly necessary and the potential benefits to the patient outweigh the possible risk to the foetus. If ibuprofen is used by a woman attempting to conceive (see section 4.6 Fertility, Pregnancy and Lactation – Effects on Fertility), or during the first or second trimester of pregnancy, the dose and duration of treatment should be kept as low and as short as possible.

During pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Inhibition of platelet aggregation;
- Renal dysfunction and impairment, which may progress to renal failure with oligohydramnios.

Prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time;
- Inhibition of platelet aggregation;
- Inhibition of uterine contractions, which may result in delayed or prolonged labour.

When given during the latter part of pregnancy, ibuprofen may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Opioid analgesics cross the placenta. Administration of codeine during labour may cause respiratory depression in the newborn infant. Regular use of codeine during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. Codeine may cause respiratory depression and withdrawal symptoms in the neonates born to mothers who use codeine during pregnancy.

*Category C:*

*Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying text above should be consulted for further details.*

**Use in lactation.**

Ibudeine is contraindicated during breast-feeding (see section 4.4 Special warnings and precautions for use – CYP2D6 Metabolism) due to the risk of respiratory depression in the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breast-feeding mothers taking codeine may have an 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 breast-fed 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, Ibudeine is contraindicated for use during breast-feeding. However, in circumstances where a breast-feeding mother requires codeine therapy, breast-feeding 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

IBUDEINE may cause sedation in some patients and the reaction time of patients may be affected. IBUDEINE 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 vehicles, operate machinery or engage in activities which require them to be fully alert. Patients should be cautioned to abstain from alcohol.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

***Ibuprofen***

**More common reactions:**

***Gastrointestinal:*** The most commonly observed adverse events are gastrointestinal in nature. Gastrointestinal complaints include nausea, epigastric pain, heartburn, diarrhoea, abdominal distress, nausea and vomiting, dyspepsia, constipation, abdominal cramps or pain, gastrointestinal haemorrhage, melaena, fullness of the GI tract (bloating and flatulence).

***Auditory and vestibular***: Tinnitus, hearing impaired.

***Cardiovascular***: Oedema, fluid retention.

***Central nervous system:*** Dizziness, headache, nervousness.

***Dermatological***: Rash (including maculopapular type), pruritus.

***General:*** Decreased appetite, loss of appetite, fatigue

**Less common reactions:**

***Central nervous system:*** Depression, insomnia, anxiety, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma.

***Dermatological:*** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson Syndrome, alopecia.

***Gastrointestinal:*** Gastric or duodenal ulcer with bleeding and/or perforation, mouth ulceration, pancreatitis, gastritis, hepatitis, jaundice, abnormal liver function tests.

***Haematological:*** Neutropenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia and decrease in haemoglobin and haematocrit.

***Cardiovascular:*** Cardiac failure, myocardial infarction (see section 4.4 Special warnings and precautions for use - Cardiovascular Thrombotic Events)

***Vascular disorder:*** Hypertension

***Respiratory, thoracic and mediastinal disorders:*** Asthma, bronchospasm, dyspnoea

***Infections and infestations:*** Rhinitis and meningitis aseptic

***Ocular:*** Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields (see section 4.4 Special warnings and precautions for use). Visual impairment and toxic neuropathy have also been reported.

***Allergic:*** Syndrome of abdominal pain, fever, chills, nausea and vomiting, hypersensitivity, anaphylaxis.

Rarely exfoliative dermatitis and epidermal necrolysis, and rare cases of photosensitivity have been reported with ibuprofen.
Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties may also occur. These are usually transient and reversible on cessation of treatment.

***Codeine***

The most common adverse effects associated with codeine are nausea, vomiting, drowsiness, dizziness and constipation.

*Less frequent to rare side effects:*
Renal failure, uraemia, urinary retention or hesitance, cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions

***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 medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

***Treatment:***
In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26) for advice.

***Symptoms:***

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

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

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. It has an analgesic effect, which 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

**Ibuprofen:**

***Absorption:*** It is well absorbed from the gastrointestinal tract after oral administration with peak serum levels occurring after 1-2 hours.

***Distribution:*** 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.

***Protein binding:*** 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.

***Metabolism:*** 90% of ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation, to produce two metabolites - a hydroxylated compound and a carboxylated compound.

***Excretion:*** Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion.

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

**Codeine:**

***Absorption:*** 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. Analgesic action occurs in 15 to 30 minutes and analgesia is maintained up to 4-6 hours.

***Distribution:*** 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:*** Codeine is metabolised by 0- and N-demethylation in the liver (via the cytochrome P450 system) 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. Codeine can also undergo O- and N-demethylation catalysed by CYP2D6 and CYP3A4 respectively. About 8% of the general 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:*** 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.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity** – No data available

**Carcinogenicity** – No data available

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

The inactive ingredients are: lactose monohydrate, maize starch, glyceryl behenate, magnesium stearate, colloidal anhydrous silica, and OPADRY complete film coating system 04F58804 white (propriety ingredient 11793).

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 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 25°C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

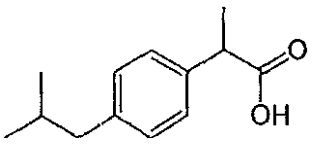
Blister packs of 24 and 30 tablets.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Ibuprofen:**



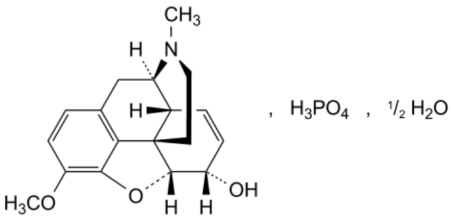
Chemical name: 2-(4-Isobutylphenyl) propionic acid.

Molecular formula: $C_{13}H_{18}O_2$.

MW: 206.3.

CAS: 15687-27-1.

**Codeine Phosphate Hemihydrate:**



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

Molecular formula: $C_{18}H_{21}NO_3.H_3PO_4 \bullet ½ H_20$.

MW: 406.4.

CAS: 41444-62-6.

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

## 8 SPONSOR

Arrow Pharma Pty Ltd

15-17 Chapel street

Cremorne, VIC 3121

## 9 DATE OF FIRST APPROVAL

23 December 2008

## 10 DATE OF REVISION

14 December 2020

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| | Addition of boxed warning |
| **4.3** | Expand respiratory contraindication |
| **4.4** | Addition of Special warnings and precautions for use |
| **4.5** | Addition of Interactions with other medicines |