NAME OF THE MEDICINE

Chemists’ Own Ibuprofen Plus Codeine

Ibuprofen 200 mg, Codeine Phosphate Hemihydrate 12.8 mg

Ibuprofen:

\[
\begin{align*}
&\text{Chemical name: } 2-(4-\text{Isobutylphenyl}) \text{ propionic acid.} \\
&M\text{olecular formula: } C_{13}H_{18}O_2. \\
&M\text{ MW: } 206.3. \\
&C\text{AS: } 15687-27-1.
\end{align*}
\]

Codeine Phosphate Hemihydrate:

\[
\begin{align*}
&\text{Chemical name: } (5R,65)-7,8\text{-didehydro-4,5-epoxy-3-methoxy-}\text{N-} \text{methyl} \text{morphinan-6-ol dihydrogen} \\
&M\text{orthophosphate hemihydrate.} \\
&M\text{ Molecular formula: } C_{18}H_{21}NO_3.H_3PO_4 \cdot \frac{1}{2} \text{H}_2\text{O}. \\
&M\text{ MW: } 406.4. \\
\end{align*}
\]

DESCRIPTION

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.

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.

The tablet contains the following active ingredients: Ibuprofen 200 mg, Codeine Phosphate Hemihydrate 12.8 mg. It also contains lactose monohydrate, maize starch, glyceryl behenate, magnesium stearate, colloidal anhydrous silica, and OPADRY white complete film coating system.

Chemists’ Own IBUPROFEN PLUS CODEINE tablets do not contain gluten or preservatives.

**PHARMACOLOGY**

**Pharmacodynamics/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.

**Pharmacokinetics**

**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.

**INDICATIONS**

Chemists’ Own IBUPROFEN PLUS CODEINE is used for temporary relief of acute moderate pain and inflammation.

**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)
- acute or pre-existing 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 Precautions – Use in Pregnancy)
- breast-feeding (see Precautions - 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 Interactions With Other Medicines)
- in patients who are:
  - CYP2D6 ultra-rapid metabolisers (see Precautions – CYP2D6 metabolism)
- younger than 12 years (see Precautions – 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 Precautions – Paediatric Use)

Refer to INTERACTIONS WITH OTHER MEDICINES for additional information.

**PRECAUTIONS**

Chemists’ Own IBUPROFEN PLUS CODEINE 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 Contraindications; also see Precautions – Impaired Liver Function or a History of Liver Disease)
- 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, myxœdema, 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 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.

Codeine should be used with caution in patients with a history of drug abuse. Physical and/or psychological dependence, including drug tolerance, may occur following prolonged administration of codeine.
Codeine may cause drowsiness; those affected should not drive, operate machinery, or drink alcohol whilst taking this medication.

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.

**Risks from Concomitant Use of Opioids and Benzodiazepines**
Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for other signs and symptoms of sedation and respiratory depression (see Interactions With Other Medicines).

**Risks from Concomitant Use of Opioids and Alcohol**
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see Interactions With Other Medicines). Use in active alcoholism is contraindicated (see Contraindications).

**CYP2D6 Metabolism**
Chemists' Own IBUPROFEN PLUS CODEINE 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 on Paediatric Use and 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. Chemists’ Own IBUPROFEN PLUS CODEINE is contraindicated in patients with heart failure (see Contraindications).

**Gastrointestinal Events**

Chemists’ Own IBUPROFEN PLUS CODEINE 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 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 Interactions With Other Medicines).
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 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 Interactions With Other Medicines).

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.

**Respiratory Disorders**

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.

**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.

**Impaired Liver Function or a History of Liver Disease**

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 Chemists' Own IBUPROFEN PLUS CODEINE is contraindicated in patients with severe hepatic impairment.

**Impaired Renal Function**
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.

**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. Chemists' Own IBUPROFEN PLUS CODEINE is contraindicated in patients with conditions involving an increased tendency of bleeding or active bleeding, such as those on anticoagulation therapy (see Contraindications and Interactions With Other Medicines).

**Masking Signs of Infection**
As with other NSAIDs, ibuprofen may mask the usual signs of infection.
**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 gastrochisis 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. Chemists’ Own IBUPROFEN PLUS CODEINE 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 Precautions – 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:
Chemists’ Own IBUPROFEN PLUS CODEINE is contraindicated during breast-feeding (see Precautions – 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 Precautions – CYP2D6 Metabolism).

Therefore, Chemists’ Own IBUPROFEN PLUS CODEINE 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.

Paediatric Use:
Chemists’ Own IBUPROFEN PLUS CODEINE 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 Precautions – CYP2D6 Metabolism.)

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.

Effect 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.
INTERACTIONS WITH OTHER MEDICINES

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. Chemists’ Own IBUPROFEN PLUS CODEINE is contraindicated in patients with conditions involving an increased tendency of bleeding or active bleeding, such as those on anti-coagulation therapy (see 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 Precautions). This includes use in fixed combination medicines containing more than one class of drug. Combined use of these medicines 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. barbiturates, chloral hydrate, sedatives, alcohol and centrally acting muscle relaxants) can cause additive CNS depression.**

- **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 Precautions).

- **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.

- **Benzodiazepines:** Concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma and death, because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Precautions).

- **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.

- **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**

- **Tranquillisers, sedatives, hypnotics, and general anaesthetics:** Codeine may potentiate the effects of these drugs. Concomitant use of tranquilisers or sedatives may enhance the potential respiratory depressant effects 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.
ADVERSE 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 Precautions - 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 Precautions). 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

**DOSAGE AND 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.

Chemists’ Own IBUPROFEN PLUS CODEINE 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 Contraindications, Precautions – Paediatric Use, and Precautions – CYP2D6 Metabolism.)

**OVERDOSAGE**

*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.

**PRESENTATION AND STORAGE CONDITIONS**

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

Pack size(s): 24s, 30s

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):
23 December 2008

DATE OF MOST RECENT AMENDMENT:
13 November 2017

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