

CORE PRODUCT INFORMATION for IBUPROFEN/CODEINE COMBINATION ANALGESIC

Product description

This section should include:

- *a description of the dosage form;*
- *a list of the active ingredients, using Australian Approved Names (AANs) and expressed quantitatively; and*
- *a list of the excipients, using Australian Approved Names (AANs) and expressed qualitatively*

Pharmacology

Pharmacokinetics:

Ibuprofen is well absorbed from the gastrointestinal tract. It is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation. 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. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

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.

Codeine is metabolised by *O*- and *N*-demethylation in the liver (via the cytochrome P450 system) to morphine (about ten per cent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Approximately 3% to 16% of a dose is eliminated unchanged in the urine.

About 8% of people metabolise drugs poorly via CYP2D6, and are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine.

The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

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.

Indications

This section must contain the indications of the product as specified in the ARTG. If the indications are not specified in the ARTG (e.g. for a non-validated grandfathered product), the indications must be as specified on an approved product label.

It should be noted that, if labels of grandfather products have not been approved by the TGA or the ARTG indications have not been validated through OPAL, then the PI will require evaluation.

Contraindications

[*Product name*] is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to ibuprofen, aspirin, other NSAIDs, codeine or other opiates (or any of the other ingredients in the product):

It is also contraindicated for use in patients:

- with active gastrointestinal bleeding or peptic ulceration
- with acute respiratory depression
- with chronic constipation
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate
- with active alcoholism
- with diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).

Use of ibuprofen is contraindicated during the third trimester of pregnancy.

[*Product name*] should not be taken with other products containing ibuprofen, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction.

Refer to 'Interactions with other medicines' for additional information

Precautions

[*Product name*] should be used with caution in patients with:

- previous history of gastrointestinal haemorrhage or ulcers
- asthma who have not previously taken a non-steroidal anti-inflammatory drug (NSAID)
- pregnancy (see use in pregnancy)
- hepatic, renal or cardiac impairment

- decreased respiratory reserve e.g. asthma or chronic obstructive pulmonary disease (COPD)
- pre-existing respiratory depression
- raised intracranial pressure or head injury
- prostatic hypertrophy
- hypotension
- hypothyroidism

It should also be used with caution in patients who:

- have a history of drug abuse
- are taking other respiratory depressants or sedatives, including alcohol
- have had recent gastrointestinal tract surgery

Codeine may obscure the diagnosis or the course of gastrointestinal diseases.

Prolonged use of codeine may produce physical and psychological dependence.

Codeine may cause drowsiness. Those affected should not drive or operate machinery.

Refer to 'Interactions with other medicines' for additional information.

Use in pregnancy

Category C: Ibuprofen inhibits prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and may delay labour and birth.

Opioid analgesics may cause respiratory depression in the newborn infant. Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate.

Use of [*Product name*] is thus contraindicated during the third trimester of pregnancy, including the last few days before expected birth.

Further, there is insufficient experience with the safety of use of ibuprofen in humans during pregnancy. [*Product name*] should therefore not be used during the first 6 months of pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

Use in lactation

Ibuprofen and codeine both appear in breast milk in low concentrations. Codeine may cause respiratory depression in newborn infants.

[*Product name*] is therefore not recommended for breastfeeding mothers unless the potential benefits to the patient outweigh the possible risk to the infant.

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.

Interaction with other medicines

The following interactions have been noted:

- anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
 - Ibuprofen may decrease renal clearance and increase plasma concentration of lithium
 - Ibuprofen may reduce the anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments
 - Ibuprofen reduces methotrexate clearance
 - Ibuprofen may increase plasma levels of cardiac glycosides
 - Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids
 - Ibuprofen may prolong bleeding time in patients treated with zidovudine
 - Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.
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- 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
 - 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) – concurrent administration or use within 14 days of ceasing MAOIs may enhance the potential respiratory depressant effects of codeine
 - 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 and hypnotics – codeine may potentiate the effects of these substances

Adverse reactions

Adverse effects with non-prescription (OTC) or short-term use ibuprofen are rare and may include:

- gastrointestinal – dyspepsia, heartburn, nausea, loss of appetite, stomach pain, diarrhoea
- central nervous system (CNS) – dizziness, fatigue, headache, nervousness
- hypersensitivity reactions - skin rashes and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.
- rare cases of photosensitivity
- cardiovascular - fluid retention and in some cases oedema. These effects are rare at non-prescription doses

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.

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

Other side effects include: cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

Dosage

This section must contain the current dosage instructions of the registered product, as specified on the product label. Non-validated grandfathered products will have to undergo full evaluation by the TGA.

Overdosage

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126; in New Zealand call 0800 764 766) for advice.

Presentation

Information should be included on:

- *the presentation, including dosage form and pack sizes;*
- *identifying details (eg. colour, shape, identifying markings);*
- *poisons schedule details; and*
- *name and address of the sponsor*

Include the date of approval.