

CORE PRODUCT INFORMATION for ASPIRIN/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:

Aspirin: Aspirin is absorbed rapidly from the gastrointestinal tract when taken orally.

*This paragraph only to be used for **non-enteric coated products**:* Absorption of non-ionised aspirin occurs in the stomach and intestine. The rate of absorption is dependent upon factors as stomach content, gastric emptying times, tablet disintegration rates and gastric pH. Some aspirin is hydrolysed to salicylate in the gut wall.

*This paragraph only to be used for **enteric coated products**:* After oral administration, aspirin is released when the pH is >6 in the small intestine. The stomach is not exposed to the local effects of aspirin.

Once absorbed, aspirin is rapidly converted to salicylate, with peak levels after 20-30 minutes. Salicylate is converted mainly in the liver to three main metabolic products: salicyluric acid, salicylic phenolic glucuronide and salicylic acyl glucuronide. A small amount of gentisic acid is also formed. The salicylate and its metabolites are excreted mainly by the kidneys. The rate of excretion increases with larger doses and also varies with the pH of the urine, increasing as the pH rises.

Excretion occurs with a half-life between 2 and 19 hours, depending on the dose of aspirin administered.

Codeine: Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma-codeine concentrations occur at about one hour after ingestion of codeine phosphate.

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:

Aspirin inhibits prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX-1 and COX-2). The resulting decrease in prostaglandin reduces the sensitivity of pain receptors to the initiation of pain impulses at sites of inflammation and trauma. Although some evidence suggests that aspirin also produces analgesia through a central mechanism, its site of action is primarily peripheral.

This results in its anti-inflammatory, analgesic and antipyretic effects. Although both aspirin and salicylate have pharmacological activity, only aspirin has an anti-platelet effect, the result of inhibition of the prostaglandin thromboxane.

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 the 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 in patients with known allergy or hypersensitivity to aspirin or other salicylates, NSAIDs, codeine or other opiates or any other ingredients in the product.

Aspirin is contraindicated for use in patients with:

- bleeding disorders, such as haemophilia
- severe hepatic disease
- kidney disease
- peptic ulcer or erosive gastritis

Codeine is contraindicated for use in people:

- 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).

Refer to 'Interactions with other medicines' for additional information

Precautions

Concomitant use of [*Product name*] with other salicylate containing preparations, non-steroidal anti-inflammatory drugs (NSAIDs) or uricosuric agents may increase the risk of gastric irritation.

It should be used with caution in people with hepatic impairment.

Aspirin should be used with caution in people with asthma or allergic disorders.

Concurrent ingestion of aspirin and alcohol may enhance occult blood loss and gastric damage.

Aspirin should be used with caution in people who have a previous history of gastrointestinal haemorrhage or ulcers. Even though food delays gastric emptying and hence the absorption of aspirin, it is preferable to take aspirin with or immediately after food to minimise gastric irritation.

Because of its anti-platelet effects, aspirin should be stopped several days before scheduled surgical procedures.

Codeine should be used with caution in people with:

- 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 people 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)

Aspirin 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.

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

There is also insufficient experience about the safety of use of aspirin in humans during pregnancy. [*Product name*] should not be used during the first 6 months of pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

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 in lactation

Aspirin and codeine both appear in breast milk. Codeine may also 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 children

Aspirin should only be given on the advice of a doctor to:

- children under 12 years of age
- children or adolescents under 16 years of age with or recovering from viral conditions such as chicken pox, influenza or fever because of its suspected link with Reyes syndrome.

Use in the elderly

Care should be taken when using in the elderly.

Adults over the age of 65 may be at an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment. They may also be more susceptible to the respiratory depressant effects of codeine.

Interaction with other medicines

The following interactions have been noted:

- Alcohol – concurrent ingestion of alcohol and aspirin may enhance gastric irritation. The CNS depressant effects of alcohol may be enhanced by codeine.
- Anticoagulants – aspirin may affect the coagulation process and should not be taken by patients on anticoagulants
- Diphenylhydantoin, sodium valproate, sulfonamides and methotrexate – aspirin can displace these drugs from protein binding sites thereby enhancing their effect.
- The activity of methotrexate may be markedly enhanced and its toxicity increased by administration with aspirin.
- Probenecid – aspirin reduces the actions of uricosuric agents such as probenecid
- Sulfonyleureas – high doses of aspirin enhance the hypoglycaemic effects of sulfonyleureas, e.g. chlorpropamide

- Caffeine – caffeine increases aspirin absorption
- Urinary alkalinisers increase the rate of excretion of aspirin
- Spironolactone – aspirin antagonises the diuretic effect of spironolactone
- Hydrocortisone – may increase the renal clearance of salicylate. When hydrocortisone is discontinued, serum salicylate levels may increase significantly
- CNS depressants – concomitant use of codeine with central nervous system depressants (e.g. barbiturates, sedatives, muscle relaxants, general anaesthetics, and other 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 aspirin may include:

- Gastrointestinal – dyspepsia, heartburn, nausea and vomiting. Less commonly, irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur
- Hypersensitivity – urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often exhibit cross-sensitivity to other NSAIDs
- Mild chronic salicylate intoxication, or salicylism, may occur after repeated use of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage
- Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders
- The use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children.

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 (e.g. colour, shape, identifying markings);*
- *poisons schedule details; and*
- *name and address of the sponsor*

Include the date of approval.