PRODUCT INFORMATION

Name of Drug

Aspalgin tablets contain aspirin 300 mg (as dispersible aspirin) and codeine phosphate 8 mg.

Description

Aspirin exists as colourless or white crystals or white crystalline powder. It is odourless or almost odourless. It is slightly soluble in water, freely soluble in alcohol, soluble in chloroform and ether.

Aspirin has the molecular formula \( \text{C}_9\text{H}_8\text{O}_4 \). It has a molecular weight of 180.2. (CAS - 50-78-2). It has the following chemical structure:

![Aspirin Chemical Structure](attachment:image)

Codeine phosphate is a small, colourless, odourless crystal or a white, odourless crystalline powder. Codeine phosphate is soluble in 4 parts of water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

Codeine phosphate is \((5R,6S)-7,8\)-didehydro-\(4,5\)-epoxy-3-methoxy-\(N\)-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate.

The molecular formula is \( \text{C}_{18}\text{H}_{21}\text{NO}_3\cdot\text{H}_3\text{PO}_4\cdot1/2\text{H}_2\text{O} \). The molecular weight is 406.4. (CAS - 41444-62-6). It has the following chemical structure:

![Codeine Phosphate Chemical Structure](attachment:image)

Aspalgin tablets contain the following excipients: starch - wheat, calcium - carbonate, citric acid, disodium edetate, sodium lauryl sulfate, talc - purified, saccharin sodium.
Pharmacology

Actions:
Aspirin is a potent inhibitor of prostaglandin synthesis through its irreversible blocking of the cyclooxygenase enzyme. This action on prostaglandins (including thromboxane A_2) contributes to its antiplatelet activity and its anti-inflammatory, analgesic and antipyretic actions. The analgesic properties of aspirin are mainly peripheral through blocking of pain impulse generation although a central action, possibly in the hypothalamus, is also likely. The anti-inflammatory action is also peripheral, due to inhibition of prostaglandin synthesis at the site of injury and a reduction in the prostaglandin mediated inflammatory response. The antipyretic effect may involve a central action of the hypothalamic heat-regulating centre to produce peripheral vasodilatation and subsequent heat loss. The anti-platelet effect is due to irreversible blockade of cyclooxygenase in platelets, necessary for the formation of the aggregating agent, thromboxane A_2.

Codeine phosphate is an opioid analgesic which binds with stereospecific receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to pain. There are multiple sub-types of opioid receptors, each mediating various therapeutic and/or side effects of drugs. Codeine has about one-sixth the analgesic activity of morphine.

It has been shown that the analgesic effects of aspirin and codeine are additive due to their different mechanisms of action.

Pharmacokinetics:
After oral administration, aspirin is absorbed partly from the stomach but mainly from the upper part of the small intestine. Aspirin has a very short elimination half-life (30 minutes) as it is rapidly hydrolysed to the therapeutically important salicylate. This conversion occurs in many tissues, particularly the G.I. mucosa and the liver. With low doses of aspirin, the salicylate has a half-life of 2-3 hours. In the liver, salicylate is converted to salicyluric acid and glucuronide conjugates. Excretion occurs mainly by the kidney. Salicylates are extensively bound to plasma proteins, particularly albumin (80-90%). Salicylates cross the placenta and are excreted in breast milk. The rate of excretion of aspirin varies with the pH of the urine, increasing as the pH rises.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1 hour after oral administration. It is metabolised in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney within 24 hours, mainly as conjugates with glucuronic acid. The plasma half life is 3-4 hours, after oral or intramuscular administration.

Indications
For the temporary relief of pain and discomfort associated with migraine headache, earache, period pain, rheumatic pain. Reduces fever and inflammation.
Contraindications

- Aspirin is contraindicated in patients with bleeding disorders; severe hepatic disease; kidney disease; uraemia; erosive gastritis; peptic ulcer; asthma; hypersensitivity to salicylates, including aspirin; or in patients taking anticoagulant therapy.
- Codeine should not be used in acute respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, since codeine may exacerbate the condition; after operations on the biliary tract as codeine may cause biliary contraction; in the presence of acute alcohol intoxication, head injuries and conditions in which intracranial pressure is raised; bronchial asthma attack or in heart failure secondary to chronic lung disease.
- Codeine is contraindicated in patients taking MAOI’s or within ten days of stopping such treatment.
- Due to codeine’s structural similarity to morphine and oxycodone, patients experiencing systemic allergy (generalised rash, shortness of breath) to these drugs should not receive codeine.
- Codeine is contraindicated in patients with diarrhoea caused by poisoning, until the toxic substance has been eliminated from the gastrointestinal tract, or diarrhoea associated with pseudomembranous colitis caused by antibiotic administration since codeine may slow the elimination of the toxic material or antibiotic.
- Aspalgin is contraindicated in patients with a past history of allergic reactions to codeine.

Precautions

Concurrent use of alcohol and aspirin may increase gastric irritation and occult blood loss, which may lead to iron deficiency anaemia with prolonged use. Concurrent use of NSAIDs may increase the risk of gastric ulceration. Because of its anti-platelet effects it may be advisable to withdraw aspirin prior to surgery.

Caution is necessary when renal function is impaired; prolonged administration of large doses of aspirin has been associated with renal papillary necrosis.

Codeine should be used with caution in patients with head injuries (due to risk of respiratory depression), inflammatory bowel disease or recent G.I. tract surgery.

Codeine should be used with caution in elderly or debilitated patients because of the danger of respiratory or cardiac depression.

Codeine should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, impaired hepatic function, or shock.

Codeine should be administered with caution in patients with prostatic hypertrophy, urethral stricture or recent urinary tract surgery since codeine may cause urinary retention.

Patients should be warned that codeine might impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).
Codeine should be used with caution in patients with a history of drug abuse or dependence, including alcoholism.

Prolonged use of high doses of codeine has produced dependence of the morphine type in a very small proportion of users. Codeine produces less euphoria and sedation than morphine and is not a completely satisfactory substitute for morphine in morphine addicts. Withdrawal symptoms develop more slowly than with morphine and are milder.

**Use in Pregnancy:** Category C
Drugs which owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the foetal ductus arteriosus, delay labour and birth. Aspirin increases the bleeding time both in the newborn infant and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester.

Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate.

**Use in Lactation:**
Aspirin is excreted in breast milk in low concentrations but since neonates excrete salicylates slowly and are sensitive to aspirin it should be avoided in nursing mothers, particularly in high doses.

Codeine passes into breast milk so should be avoided in breastfeeding women.

**Use in Children:**
Aspirin and codeine are not recommended for children, except under medical supervision. The use of aspirin in children and adolescents has been implicated in some cases of Reye's Syndrome and paediatric use is not recommended, particularly during viral illness.

**Use in Geriatrics:**
The elderly are more likely to have age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

**Carcinogenicity, Mutagenicity, Impairment of Fertility:**
No significant effects have been reported.

**Interactions with Other Drugs**

*Food:* Food delays gastric emptying and hence the absorption of aspirin; nevertheless it may be preferable to take aspirin with food in order to minimise gastric irritation.

*Alcohol:* Concurrent ingestion of alcohol and aspirin may enhance gastric irritation. The CNS depressant effects of alcohol may be enhanced by codeine.
Anti-coagulants: Aspirin may affect the coagulation process and should be avoided in patients on anti-coagulants.

Diphenylhydantoin, Sodium valproate, Sulphonamides 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: Low dose aspirin reduce the actions of uricosuric agents such as probenecid.

Sulphonylureas: High doses of aspirin enhance the hypoglycaemic effects of sulphonylureas. Caffeine: Caffeine increases aspirin absorption while urinary alkalinisers increase the rate of excretion.

Spironolactone: Aspirin antagonises the diuretic effect of spironolactone.

General anaesthetics: Codeine may potentiate the effects of general anaesthetics.

CNS depressants (such as anaesthetics, hypnotics, sedatives and phenothiazines): Codeine may potentiate the depressant effects of CNS depressants.

Opioid analgesics: Codeine may potentiate the effects of opioid agonists.

Antihistamines: Concomitant use of codeine and antihistamines with anticholinergic effects may result in an increased risk of severe constipation and/or urinary retention. Codeine may potentiate the CNS depressant effects of certain antihistamines.

Monoamine Oxidase Inhibitors: Serious and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAO inhibitors or within 14 days of stopping such treatment. Caution is advised with the combination of codeine and selective MAO inhibitors (reversible inhibitors of Monoamine Oxidase A).

Quinidine: Quinidine interferes with the metabolism of codeine to morphine lowering the analgesic effect of codeine.

Cimetidine: Cimetidine may reduce the metabolism of codeine, enhancing the possibility of codeine toxicity.

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.
Adverse Reactions

**Common**

_Gastro intestinal_
- Nausea
- Dyspepsia
- Vomiting.
- Constipation

_Less frequent to rare_
- Irritation of the gastric mucosa with erosion, ulceration, haematemesis and melaena

**Hypersensitivity***

_Less frequent to rare_
- Urticaria and other skin eruptions
- Angioedema
- Rhinitis
- Severe, even fatal, paroxysmal bronchospasm and dyspnoea.

(*More common in asthmatics)

**CNS Effects**

_Common_
- Drowsiness
- Dizziness
- Tinnitus

_Other_

_Common_
- Sweating

Dosage and Administration

Tablets should be dissolved in a little water before taking.

**Adults and children 12 years and over:**
2 tablets every four hours or as directed, to a maximum of 8 tablets per day.

**Children:** Not recommended for use in children under 12 years of age.

This medication is not recommended for use in children and teenagers with chickenpox, influenza or fever.

Overdosage

In cases of overdosage, contact the National Poisons Information Centre on telephone number 13 11 26. Overdosage with Aspalgin tablets involves treatment of both aspirin and codeine poisoning.

**Aspirin:**

_Symptoms_ - Mild chronic salicylate intoxication usually occurs only after repeated administration of large doses. Symptoms include: dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache and mental confusion, may be controlled by reducing the dose.
Symptoms of more severe intoxication or of acute poisoning following overdosage include: hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis. Depression of the central nervous system may lead to coma, cardiovascular collapse, and respiratory failure. In children, drowsiness and metabolic acidosis commonly occur, hypoglycaemia may be severe.

_Treatment_ - In acute salicylate overdosage, the stomach should be emptied by aspiration and lavage. Patients with mild intoxication should be encouraged to increase fluid intake. In patients with more severe intoxication, forced alkaline diuresis may be required. Plasma electrolytes, particularly potassium, and the acid-base balance should be monitored regularly. In the presence of cardiac or renal function impairment or in very severe intoxication, haemodialysis or haemoperfusion may need to be considered.

**Codeine:**

_Symptoms_ - Symptoms of codeine overdosage include vomiting, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

_Treatment_ - Support respiratory and cardiovascular function. Assisted ventilation may be necessary. Induction of emesis is not recommended because of the potential for CNS depression and seizures. Administer activated charcoal, taking care to protect the airway as necessary. If clinically significant respiratory or cardiac depression is present, give naloxone. The usual adult dose is 0.4 – 2.0 mg intravenously (or subcutaneously), repeated every 2 to 3 minutes if necessary up to 10 mg. The use of naloxone in physically dependent patients may precipitate withdrawal symptoms.

**Presentation**

Tablets (white, effervescent, marked FM): 20's, 50's, 100's.

**Storage**

Store below 25°C. Protect from light and moisture.

**Poisons Schedule**

20’s: PHARMACY MEDICINE - S2 (All States and A.C.T.)
50’s, 100’s: PHARMACY MEDICINE – S2 (N.S.W.)
PHARMACIST ONLY MEDICINE - S3 (Other States and A.C.T.)
Sponsor

Aspen Pharma Pty Ltd
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Australia

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