AUSTRALIAN PRODUCT INFORMATION

ASPALGIN®

aspirin and codeine phosphate hemihydrate dispersible tablets

WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, ASPALGIN 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
ASPALGIN 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 ASPALGIN. 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 ASPALGIN.

1 NAME OF THE MEDICINE

Aspirin and codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ASPALGIN dispersible tablet contains 300 mg aspirin and 8 mg codeine phosphate hemihydrate as the active ingredients.

Excipients of known effect: gluten, saccharin.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ASPALGIN dispersible tablets are round, white and flat with bevelled edges with one side plain and one side engraved FM having a diameter of 17/32".

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the temporary relief of acute moderate pain, inflammation and fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

ASPALGIN dispersible 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 for use in children as follows:

- younger than 12 years (see Section 4.3 CONTRAINDICATIONS)
- 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 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use)

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

4.3 CONTRAINDICATIONS

ASPALGIN is contraindicated in patients with known hypersensitivity to aspirin, salicylates, codeine or any of the excipients used in the product.

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.

Due to the codeine content, ASPALGIN is contraindicated in the following conditions:

- severe respiratory disease, acute respiratory disease and respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, since codeine may exacerbate the condition
- bronchial asthma attack or in heart failure secondary to chronic lung disease
- 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
- in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment
- 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

Due to the aspirin content, ASPALGIN is contraindicated in patients with:

- bleeding disorders
- severe hepatic disease
- kidney disease
- uraemia
- erosive gastritis
- peptic ulcer

- taking anticoagulant therapy

ASPALGIN is contraindicated for use 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 and 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)

- breastfeeding (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Lactation)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and Harmful Use

ASPALGIN contains the opioid codeine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed codeine 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 ASPALGIN.

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 ASPALGIN 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 ASPALGIN 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 and in patients with existing impairment of hepatic, renal or 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.

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 ASPALGIN 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 ASPALGIN 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 ASPALGIN.

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 ASPALGIN 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 ASPALGIN, especially by children, can result in a fatal overdose of codeine. Patients and their caregivers should be given information on safe storage and disposal of unused ASPALGIN (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.

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.

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

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

CYP2D6 Metabolism

ASPALGIN 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 into 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% to 10% in Caucasians. The highest prevalence (16% to 28%) occurs in North African, Ethiopian and Arab populations.

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use and Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation.

Use in Hepatic Impairment

Codeine should be given with caution or in reduced doses to patients with impaired hepatic function.

Use in Renal Impairment

Caution is necessary when renal function is impaired. Opioids and their metabolites are excreted primarily via the kidneys. Because of this there is an increased risk of adverse effects in patients with renal function impairment. Prolonged administration of large doses of aspirin has been associated with renal papillary necrosis.

Use in the Elderly

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

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.

Paediatric Use

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.

ASPALGIN is contraindicated for use in children:

- younger than 12 years
- aged between 12 to 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 a CYP2D6 polymorphism.

See 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

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 such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Risks from Concomitant Use of Benzodiazepines or Other CNS Depressants, Including Alcohol).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy category: C

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the fetal 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 fetus, 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.

ASPALGIN is contraindicated during breastfeeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - CYP2D6 Metabolism) due to risk of respiratory depression in the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breastfeeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultrarapid metaboliser of codeine. Codeine is excreted into human breast milk. Codeine is partially metabolised by cytochrome P4502D6 (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 breastfed 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, ASPALGIN is contraindicated for use during breastfeeding. However, in circumstances where a breastfeeding mother requires codeine therapy, breastfeeding should be suspended, and alternative arrangements should be made for feeding the infant for any period during codeine treatment. Breastfeeding 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

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). This medication may cause drowsiness. If affected, patients should not drive a vehicle or operate machinery. Avoid alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal	
Common	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
CNS Effects	
Common	Drowsiness Dizziness Tinnitus
Other	
Common	Sweating

* more common in asthmatics

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

4.9 OVERDOSE

Overdosage with ASPALGIN 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. 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 to 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.

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

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

Aspirin

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

Codeine 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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Aspirin

After oral administration, aspirin is absorbed partly from the stomach but mainly from the upper part of the small intestine.

Codeine

Codeine is absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1 hour after oral administration.

Distribution

Aspirin

Salicylates are extensively bound to plasma proteins, particularly albumin (80% to 90%). Salicylates cross the placenta and are excreted in breast milk.

Metabolism

Aspirin

Aspirin 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 to 3 hours. In the liver, salicylate is converted to salicyluric acid and glucuronide conjugates.

Codeine
The plasma half-life is 3 to 4 hours, after oral or intramuscular administration. It is metabolised in the liver to morphine and norcodeine.

Excretion

Aspirin

Aspirin has a very short elimination half-life (30 minutes). Excretion occurs mainly by the kidney. The rate of excretion of aspirin varies with the pH of the urine, increasing as the pH rises.

Codeine

Codeine and its metabolites are excreted almost entirely by the kidney within 24 hours, mainly as conjugates with glucuronic acid.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ASPALGIN contains the following excipients: calcium carbonate, citric acid, disodium edetate, purified talc, saccharin sodium, sodium lauryl sulfate and wheat starch.

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. Store in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (PA/Al/PVC/Al)

Pack sizes: 20, 40

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 13431 – ASPALGIN aspirin 300 mg codeine phosphate hemihydrate 8 mg dispersible tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

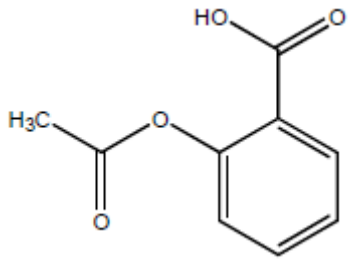
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Aspirin

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.



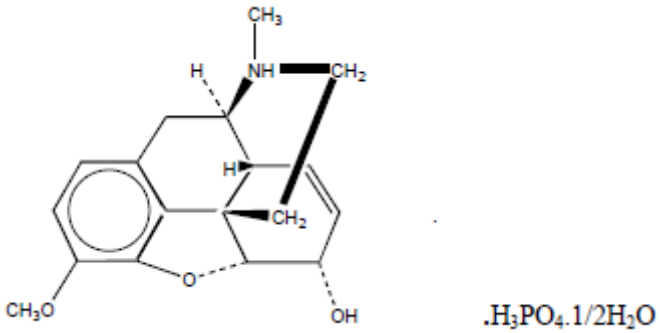
Chemical name: salicylic acid acetate

Molecular formula: $C_9H_8O_4$

Molecular weight: 180.2

Codeine Phosphate Hemihydrate

Codeine phosphate hemihydrate 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.



$.H_3PO_4.1/2H_2O$

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

Molecular formula: $C_{18}H_{21}NO_3.H_3PO_4.1/2H_2O$

Molecular weight: 406.4

CAS Number

Aspirin: 50-78-2

Codeine phosphate hemihydrate: 41444-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

30/08/1991

10 DATE OF REVISION

11/04/2022

Summary Table of Changes

Section Changed	Summary of New Information
3, 4.2	Minor editorial update
6.5	Insert AUST R numbers
8	Update sponsor's details

ASPALGIN® is a Viatris company trade mark

ASPALGIN_pi\Apr22/01