AUSTRALIAN PRODUCT INFORMATION

CODALGIN® FORTE

(paracetamol & codeine phosphate hemihydrate) tablet

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, CODALGIN FORTE 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

CODALGIN FORTE 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 CODALGIN FORTE. 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 CODALGIN FORTE.

1 NAME OF THE MEDICINE

Paracetamol and codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CODALGIN FORTE tablet contains 500 mg of paracetamol and 30 mg of codeine phosphate hemihydrate as the active ingredients.

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

3 PHARMACEUTICAL FORM

A 16.8 mm x 7.7 mm white, capsule-shaped tablet, plain on one side and with a breakbar on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CODALGIN FORTE is indicated for the short-term management of severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years of age and over: 1 or 2 tablets every 4 to 6 hours if necessary for relief of severe pain. Do not exceed 8 tablets in a 24-hour period.

Children under 12 years of age: see section 4.3 CONTRAINDICATIONS.

Tablets to be taken with water.

4.3 CONTRAINDICATIONS

CODALGIN FORTE

CODALGIN FORTE must not be used in patients with known hypersensitivity to paracetamol, codeine or any of the excipients used in this product.

CODALGIN FORTE must not be used in patients with known glucose-6-phosphate-dehydrogenase deficiency or severe respiratory disease, acute respiratory disease (e.g. acute asthma, acute exacerbations of chronic obstructive pulmonary disease) and respiratory depression, since codeine may exacerbate the condition.

CODALGIN FORTE 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 12-18 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).

Paracetamol

Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion predisposes patients to paracetamol hepatotoxicity.

Paracetamol should not be used in patients with a history of intolerance or hypersensitivity to the drug.

Paracetamol should not be used in patients with severe hepatocellular insufficiency.

Codeine

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.

Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth (see section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and Harmful Use

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

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

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 sections 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 CODALGIN FORTE 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 CODALGIN FORTE 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, in patients with hepatic and renal impairment (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in Hepatic Impairment and Use in Renal Impairment) and in patients with existing impairment of 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 CODALGIN FORTE 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 CODALGIN FORTE 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 CODALGIN FORTE.

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

Opioid-Induced Hyperalgesia or Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

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.

CYP2D6 Metabolism

CODALGIN FORTE 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%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations.

(See also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use and section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Lactation.)

Other Information

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. In view of the increased risk of hepatotoxicity, the benefit should be weighed against the risk when administering CODALGIN FORTE to patients with viral hepatitis or pre-existing hepatic disease. In such patients, hepatic function determinations may be required at periodic intervals during high dose or long-term therapy.

To avoid the risk of overdose check that paracetamol is absent from the composition of other medicinal products taken concomitantly.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Severe cutaneous adverse reactions (SCARs): Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop paracetamol treatment immediately and seek medical advice.

Paracetamol should be used with caution in patients with:

- recent cessation of alcohol intake
- low glutathione reserves
- Gilbert’s syndrome

Codeine should be administered with great caution in patients with CNS depression or decreased respiratory reserve e.g. in emphysema, kyphoscoliosis, hypoxia, hypercapnia, even severe obesity, cor pulmonale, or chronic obstructive pulmonary disease since codeine may exacerbate respiratory impairment and CNS depression. Codeine should be administered with caution in patients with impaired cardiac, hepatic or renal function, hypotension, benign prostatic hyperplasia, urethral stenosis, chronic ulcerative colitis, gall bladder conditions, multiple sclerosis, hypothyroidism, adrenocortical insufficiency (e.g. Addison’s disease), shock, myxoedema, acute alcohol intoxication or delirium tremens since codeine may exacerbate the symptoms or increase the risk of respiratory and/or CNS depression.

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.

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.

Monitoring after prolonged use should include blood count, liver function and renal function.

Codeine should only be used with careful risk-benefit assessment and great caution in case of:

- Opioid dependence
- Chronic constipation
- Conditions with elevated intracranial pressure and head trauma. Codeine can increase the pressure of cerebrospinal fluid and may increase the respiratory depressant effect. Like other narcotics, it causes adverse reactions that can obscure the clinical course of patients with head injury.
- Impaired consciousness
- Compromised respiratory function (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airway disease

Patients with known analgesic intolerance or known bronchial asthma must only use CODALGIN FORTE after having consulted their doctor, given the possibility of hypersensitivity reactions including bronchospasm.

Codeine should be administered with caution in patients with acute abdominal conditions since codeine may obscure the diagnosis or the course of the disease. Codeine should be administered with caution in patients with severe inflammatory bowel disease (risk of toxic megacolon may be increased, especially with repeated dosing). Codeine should be used with caution in patients with recent gastrointestinal tract surgery.

Patients who have had a cholecystectomy should be treated with caution. The contraction of the sphincter of Oddi can cause symptoms resembling those of myocardial infarction or intensify the symptoms in patients with pancreatitis.

Codeine should be administered with caution in patients with a history of convulsive disorders (convulsions may be induced or exacerbated by codeine).

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

Codeine should be administered with caution in patients taking Monoamine Oxidase Inhibitors (MAOI's) – see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin) increases the risk of respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect.

Use in Hepatic Impairment

CODALGIN FORTE should be given with care to patients with impaired hepatic function, viral hepatitis, and to patients taking other drugs which affect the liver.

Use in Renal Impairment

CODALGIN FORTE should be given with care to patients with impaired renal function.

Use in the Elderly

Elderly people may be more sensitive to the effects of this medicinal product. The elderly are more likely to have hypertrophy, prostatic obstruction and age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

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

Paediatric Use

CODALGIN FORTE 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 a CYP2D6 polymorphism (See also 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.

Uric Acid and Blood Glucose

Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Salicylates and NSAIDs

Prolonged concurrent use of paracetamol and salicylates or non-steroidal anti-inflammatory drugs may increase the risk of adverse renal effects.

Coumarins

Repeated high doses of paracetamol increase the risk of bleeding in patients taking warfarin and other coumarin derivatives (antivitamin K). Monitoring of coagulation and bleeding complications is required.

Chloramphenicol

Paracetamol may also increase chloramphenicol concentrations by slowing down the excretion of chloramphenicol, thereby increasing the risk of toxicity.

Diflunisal

Diflunisal may increase the plasma concentrations of paracetamol by 50%.

Anticholinergics

Concomitant use of codeine and anticholinergic agents (including propantheline) may increase the risk of severe constipation and/or urinary retention. Drugs which decrease gastric emptying may decrease the absorption of paracetamol.

Cholestyramine

Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration.

Chelating Resin

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously.

Propantheline

Decreases gastric emptying which may decrease the absorption of paracetamol.

Rifampicin

Concomitant use may increase the likelihood of paracetamol toxicity (see Hepatotoxic drugs and liver microsomal enzymes below).

Flucloxacillin

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

General Anaesthetics

Codeine may potentiate the effects of general anaesthetics.

CNS Depressants

Codeine may potentiate the effects of CNS depressants.

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety agents, gabapentinoids, cannabis and centrally-active anti-emetics or other CNS depressants (including alcohol) concomitantly with paracetamol/codeine 500/30 may experience addictive CNS depression (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol.).

Alcohol

Codeine may potentiate the effects of alcohol and the likelihood of paracetamol toxicity may be increased by its concomitant use (see Hepatotoxic drugs and liver microsomal enzymes below). 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metoclopramide

Codeine may antagonise the effects of metoclopramide on gastrointestinal motility. Paracetamol absorption is increased by drugs which increase gastric emptying.

Domperidone

The absorption rate of paracetamol may be increased by domperidone.

Opioid Analgesics

Concurrent use of codeine and other opioid agonists is usually inappropriate as additive CNS depression, respiratory depressant and hypotensive effects may occur. Narcotic analgesics may decrease gastric emptying and therefore decrease the absorption of paracetamol (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol).

Morphinic Agonists-antagonists

Concomitant use of codeine with a partial agonist (e.g. buprenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

Tranquillisers, Sedatives and Hypnotics, General anaesthetics and CNS depressants

Codeine may potentiate the effects of these drugs. Concomitant use of tranquillisers or sedatives may enhance the potential respiratory depressant effects of codeine (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol).

Benzodiazepines

The concomitant use of alcohol 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatotoxic Drugs and Liver Microsomal Enzyme Inducers

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), alcohol, barbiturates and rifampicin. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Zidovudine

When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of CODALGIN FORTE and zidovudine particularly chronic or multiple-dose paracetamol, should be avoided. If chronic paracetamol and zidovudine are to be given concurrently, monitor white blood count and liver function tests, especially in malnourished patients.

Antiperistaltic Antidiarrhoeals (including kaolin, pectin, loperamide)

Concurrent use of these agents with codeine may increase the risk of severe constipation and CNS depression.

Monoamine Oxidase Inhibitors

Non-selective MAOI's 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 MAOI's or within 14 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAOI's (Reversible Inhibitors of Monoamine Oxidase A) and codeine, caution is advised with this drug combination.

Tricyclic Antidepressants

A codeine-induced respiratory depression can be potentiated by tricyclic antidepressants. (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol.)

Antihypertensives

Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.

Neuromuscular Blocking Agents

Codeine may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety agents, gabapentinoids, cannabis and centrally-active anti-emetics or other CNS depressants (including alcohol) concomitantly with CODALGIN FORTE may experience additive CNS depression. (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol.)

CYP2D6 Inhibitors

Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 Inducers

Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Gabapentinoids and Opioids

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin) increases the risk of respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Refer to section 5.3 PRECLINICAL SAFETY DATA – Carcinogenicity.

Use in Pregnancy

Pregnancy category: A

Paracetamol crosses the placenta, however problems in humans have not been documented.

Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the fetus, leading to withdrawal symptoms in the neonate. Administration of codeine during labour may cause respiratory depression in the newborn infant. Codeine may cause respiratory depression and withdrawal syndrome in neonates born to mothers who use codeine during the third trimester of pregnancy. As a precautionary measure, use of CODALGIN FORTE should be avoided during the third trimester of pregnancy and during labour.

Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth (see section 4.3 CONTRAINDICATIONS). CODALGIN FORTE should only be used during pregnancy under medical supervision if the potential benefit justifies the potential risk to the fetus. If administered during pregnancy, morphinomimetic properties of codeine should be taken into account.

Use in Lactation

CODALGIN FORTE is contraindicated during breast-feeding (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 ultra-rapid metaboliser of codeine. Codeine is excreted into human breast milk. Codeine is partially metabolized 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 Metabolism).

Therefore, CODALGIN FORTE 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. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CODALGIN FORTE may cause drowsiness, disturbances of visuomotor coordination and visual acuity and/or dizziness. Due to the preparation's sedative action, impairment of the mental and/or physical abilities required for the performance of potentially hazardous activities may occur. Children should be supervised during bike riding or other potentially hazardous activities.

Patients treated with this medication should not drive, operate machinery, or drink alcohol whilst taking this medication.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reports of adverse reactions are rare. Although the following reactions have been reported when paracetamol and codeine have been administered:

Haematologic

Less frequent to rare

- Agranulocytosis
- Anaemia
- Thrombocytopenia

Genitourinary

Less frequent to rare

- Renal failure
- Uraemia
- Urinary retention or hesitance

Hypersensitive

Less frequent to rare

- Skin rashes and other allergic reactions
- Histamine release (hypotension, flushing of the face, tachycardia, breathlessness)

Gastrointestinal

Common

- Constipation
- Nausea
- Vomiting

Neurological

Common

- Drowsiness
- Dizziness

Less frequent to rare

- Euphoria, dysphoria
- At higher doses, codeine may cause respiratory depression

Hepatic

Very rare

- Pancreatitis

Metabolism and nutrition system disorders

Not known

- Pyroglutamic acidosis, in patients with pre-disposing factors for glutathione depletion

Paracetamol has also been associated with dyspepsia, sweating, erythema, urticaria, anaphylactic shock, angioneurotic oedema, leukopenia, neutropenia and pancytopenia. Bronchospasms may be triggered in patients having a tendency of analgesic asthma. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption and cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

Haemolytic anaemia in particular in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported. Kounis syndrome and bronchospasm have also been reported.

Codeine can cause confusional state, dysphoria, seizure, headache, somnolence, sedation, miosis, tinnitus, dry mouth, pruritus, fatigue, hypotension. Visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particular sensitive patients. Long term use also entails the risk of drug dependence.

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

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzyme-inducing drugs are at an increased risk of intoxication, including fatal outcome.

Symptoms

Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma. Nausea, vomiting, anorexia, pallor and abdominal pain generally appear during the first 24 hours of overdosage with paracetamol. Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage. It can also lead to pancreatitis, acute renal failure and pancytopenia. The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (30 tablets) of paracetamol; a dose of 25 g (50 tablets) or more is potentially fatal. Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop.

In an evaluation of codeine intoxication in children, symptoms seen included: sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur.

The ingestion of very high doses of codeine can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

Treatment

Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.

Consists primarily of management of paracetamol toxicity; naloxone is the treatment of choice for codeine intoxication. In cases of overdosage, methods of reducing the absorption of ingested drug are important. Prompt administration of 50 g activated charcoal may reduce absorption.

Determinations of the plasma concentration of paracetamol are recommended.

If the history suggests that 15 g paracetamol or more has been ingested, administer one of the following antidotes:

Acetylcysteine 20% i.v

Administer 20% acetylcysteine immediately without waiting for positive urine test or plasma level results: initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50mg/kg in 500mL 5% glucose over 4 hours and 100 mg/kg in 1L 5% glucose over 16 hours. The volume of IV fluids should be modified for children; or

Oral Methionine

2.5 g immediately followed by three further doses of 2.5 g at four hourly intervals. For a 3-year-old child, 1 g methionine 4-hourly for four doses has been used.

If more than ten hours have elapsed since the overdosage was taken, the antidote may be ineffective and may exacerbate liver damage.

In general, treatment for codeine overdose should be symptomatic: re-establish adequate respiratory exchange by ensuring a clear airway and using mechanical ventilation. When treatment for paracetamol toxicity has been initiated naloxone 400 microgram may be administered SC, IM or IV; IV may be repeated at intervals of 2 to 3 minutes if necessary. Assisted respiration may be required. Further measures will depend on the severity, nature and course of clinical symptoms of intoxication and should follow standard intensive care protocols.

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

Paracetamol has analgesic and antipyretic activity similar to aspirin. The analgesic effect of paracetamol is thought to be due to inhibition of prostaglandin synthesis in the central nervous system and in the periphery, and, to a lesser extent, by blocking pain impulse generation in the periphery. The antipyretic effect is due to a central action on the hypothalamic heat- regulating centre to produce peripheral vasodilatation and subsequent heat loss.

Codeine phosphate hemihydrate is an opioid analgesic that binds with stereospecific receptors at many sites within the CNS to alter processes affecting both the perceptions 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. Its analgesic effect is thought to be due to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine. Codeine can also cause other effects e.g. CNS depression, nausea and vomiting, orthostatic hypotension and constipation.

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

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring some 30 minutes to 2 hours after ingestion. The onset of therapeutic action is 30 minutes and the duration of effect is 4 hours.

Codeine is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached one hour after oral administration. Onset of action occurs in 15-30 minutes and analgesia is maintained for 4-6 hours.

Distribution

Paracetamol is rapidly and uniformly distributed into most body tissues. It crosses the placenta and is present in breast milk.

Codeine is rapidly distributed to skeletal muscle, kidneys, liver, gastrointestinal tract, lungs, spleen and brain. It crosses the placenta and is distributed in low levels in breast milk.

Metabolism

Approximately 90-95% of the paracetamol dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite which may accumulate in overdosage is hepatotoxic and possibly nephrotoxic.

Codeine is metabolised mainly in the liver. 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. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite. About 10% of an administered dose of codeine is converted by O-demethylation to morphine which subsequently undergoes glucuronidation to morphine-3 or morphine-6 glucuronide, or N-demethylation to normorphine. Approximately

5-10% of the Caucasian population cannot convert codeine to morphine as they are deficient in the CYP2D6 enzyme. Codeine is also converted by N-demethylation to norcodeine which subsequently undergoes glucuronidation to norcodeine glucuronide or O-demethylation to normorphine.

Excretion

Approximately 85% of a dose of paracetamol is recovered from the urine within 24 hours after ingestion. About 5% is unchanged, the balance consisting mainly of the glucuronide and sulfate conjugates. The elimination half-life varies from 1 to 4 hours and may be prolonged in acute overdosage, in liver disease, the elderly and the neonate.

Codeine is excreted mainly by the kidneys as its metabolite codeine-6-glucuronide. 5-25% is excreted unchanged and approximately 10% is excreted as unchanged or conjugated morphine. The plasma half-life of codeine is 2-4 hours. Only traces of codeine and its metabolites are found in the faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Clinical toxicity studies in animals have shown that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis; the relevance of this finding to use in humans is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize starch, pregelatinised maize starch, povidone, microcrystalline cellulose, magnesium stearate, crospovidone, stearic acid and colloidal anhydrous silica.

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 CODALGIN FORTE tablets below 30°C in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

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

Pack size: 4, 10, 12 and 20 tablets

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

Australian Register of Therapeutic Goods (ARTG)

AUST R 226337 – CODALGIN FORTE codeine phosphate hemihydrate 30 mg and paracetamol 500 mg tablet blister pack

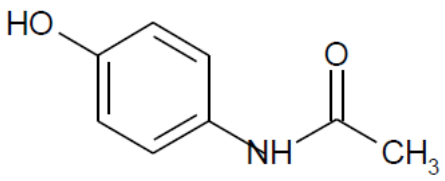
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

Paracetamol is N-(4-Hydroxyphenyl)acetamide. It has the following chemical structure:

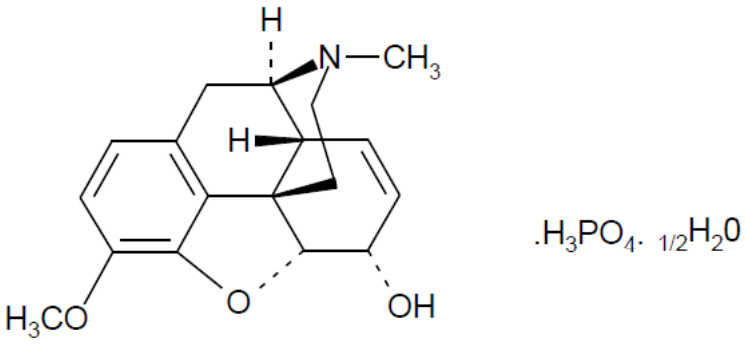


Molecular formula: $C_8H_9NO_2$

Molecular weight: 151.2

Paracetamol is a white colourless crystalline powder. It is sparingly soluble in water; soluble 1 in 20 of boiling water, and 1 in 10 of alcohol; very slightly soluble in ether and in methylene chloride. Store in airtight containers. Protect from light.

Codeine phosphate hemihydrate is (5*R*,6*S*)-7,8-didehydro-4,5-epoxy-3-methoxy-*N*-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate. It has the following chemical structure:



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

Molecular weight: 406.40

Codeine phosphate is soluble in 4 parts of water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

CAS Number

Paracetamol: 103-90-2

Codeine phosphate hemihydrate: 41444-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

3/11/2014

10 DATE OF REVISION

01/05/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Safety update to add drug-drug related interactions between opioids and gabapentinoids.
4.5	Safety update to add drug-drug related interactions between opioids and gabapentinoids.

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