

AUSTRALIAN PRODUCT INFORMATION – PRODEINE (PARACETAMOL, CODEINE PHOSPHATE HEMIHYDRATE) UNCOATED TABLET

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, Prodeine 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

Prodeine 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 Prodeine. 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 Prodeine.

1 NAME OF THE MEDICINE

Paracetamol, codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prodeine contains paracetamol 500 mg and codeine phosphate hemihydrate 9.6 mg.

Prodeine is aspirin-free.

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

3 PHARMACEUTICAL FORM

The caplets are white capsule-shaped tablets, plain on one side and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the relief of acute moderate pain and fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years of age and older: One or two caplets every 3 to 4 hours as needed for relief. Do not exceed 8 caplets in 24-hour period.

Prodeine is not recommended for use over extended periods of time.

Use in children under 12 years is contraindicated.

4.3 CONTRAINDICATIONS

Prodeine is contraindicated in patients:

- with known hypersensitivity to paracetamol, codeine or any of the excipients used in this product.
- with severe respiratory disease, acute respiratory disease and respiratory depression. for example an acute asthma attack.
- with glucose-6-phosphate-dehydrogenase deficiency.
- with severely impaired liver or renal function.

- with diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).
- with chronic constipation.
- with active alcoholism.
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in neonate.
- during breast-feeding (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in lactation)
- 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).
- who are CYP2D6 ultra-rapid metabolisers (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism).

Prodeine is contraindicated for use in patients younger than 12 years (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. This medication may be dangerous when used in large amounts or for long periods. Hepatotoxicity may develop following a dose of 10 g of paracetamol and hepatic failure is known to occur occasionally with the long term use of paracetamol.

To avoid the risk of overdose

Check that paracetamol is absent from the composition of other medicinal products taken concomitantly.

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve e.g. emphysema, kyphoscoliosis, or severe obesity.

Codeine should be administered with caution in patients with impaired cardiac, hepatic or renal function, hypotension, urethral stenosis, gallbladder conditions, multiple sclerosis, hypothyroidism, adrenocortical insufficiency, shock, acute alcohol intoxication or benign prostatic hyperplasia, hypotension, myasthenia gravis, inflammatory or obstructive bowel disorders, recent gastrointestinal tract surgery, raised intracranial pressure or head injury.

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.

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 used with caution in patients with convulsive disorders.

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 after careful risk-benefit assessment in case of:

- Opioid dependence
- 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 Prodeine after having consulted a physician (hypersensitivity reactions including bronchospasm are possible).

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 upon medical advice in patients with:

- mild to moderate hepatocellular insufficiency (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in hepatic impairment)
- severe renal insufficiency and sepsis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in renal impairment)
- chronic alcohol use including recent cessation of alcohol intake
- Malnutrition and other sources of low glutathione reserves
- Glucose-6-phosphate-dehydrogenase deficiency
- Gilbert's syndrome

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness and/or pre-disposing factors (see above) who were treated with paracetamol at therapeutic dose for a prolonged period or combination of paracetamol and flucloxacillin. Symptoms of HAGMA may include serious breathing difficulties with deep rapid breathing, drowsiness, nausea and vomiting. Prompt discontinuation of paracetamol and close monitoring is recommended if symptoms of HAGMA appear. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

CYP2D6 metabolism

Prodeine 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 CYP 2D6 in children is not known, but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers differs according to racial and ethnic group.

It 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).

Hazardous and harmful use

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

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 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 Prodeine 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 Prodeine 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 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. 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, 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 Prodeine 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 Prodeine 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 Prodeine.

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 Prodeine 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).

Accidental ingestion/exposure

Accidental ingestion or exposure of Prodeine, 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 Prodeine (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. 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.

Use in hepatic impairment

Prodeine should be used with caution in hepatic dysfunction.

Use in renal impairment

Prodeine should be used with caution in renal dysfunction.

Use in the elderly

Dosage should be reduced in elderly or debilitated patients because of the danger of respiratory or cardiac depression. Elderly people may be more sensitive to the effects of this medicinal product, especially respiratory depression. They are also more prone to suffering hypertrophy, prostatic obstruction and age-related renal impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.

Paediatric use

This product 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

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

Patients receiving other opioid analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety or other CNS depressants eg. gabapentinoids, cannabis, centrally-active anti-emetics, hypnotics, sedatives, tranquillisers, including alcohol, may exhibit an additive CNS depression and increases the risk of sedation, respiratory depression, coma and death (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.

The concomitant use of benzodiazepines 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).

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).

Concurrent administration or use within 14 days of ceasing monoamine oxidase inhibitors (MAOIs) may enhance the potential respiratory depressant effects of codeine and other side effects of unpredictable severity.

A codeine-induced respiratory depression can be potentiated by tricyclic antidepressants.

Codeine may increase the hypotensive effects of antihypertensive agents.

Other potential interactions with codeine include anticholinergic agents or antidiarrhoeal agents (due to the risk of severe constipation and CNS depression); metoclopramide (as codeine may antagonise the effects of this medicine on gastrointestinal motility); and drugs that can inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents as they can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as barbiturates and other antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol.

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

Paracetamol may considerably slow down the excretion of chloramphenicol, entailing the risk of increased toxicity. When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Prodeine and zidovudine should be avoided.

Concurrent intake of drugs, which delay gastric emptying, such as propantheline, may slow down the uptake of paracetamol, thereby retarding its onset of action. Conversely, drugs, which accelerate gastric emptying, such as metoclopramide or domperidone, may accelerate the absorption rate of paracetamol and its onset of action.

Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol. Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

Co-administration of flucloxacillin with paracetamol may lead to high anion gap metabolic acidosis due to pyroglutamic acidosis, particularly in patients with risk factors (see section 4.4).

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

No data available

Use in pregnancy

Category A.

There have been no observations of an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus in pregnant women and women of child-bearing age who have taken the active ingredients in Prodeine.

However, prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate. Opioid analgesics 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 Prodeine should be avoided during the third trimester of pregnancy and during labour. Prodeine should only be used during pregnancy under medical supervision if the potential benefit justifies the potential risk to the foetus. If administered during pregnancy, morphinomimetic properties of codeine should be taken into account.

Use in lactation

Prodeine is contraindicated during breast-feeding (see Section 4.3 CONTRAINDICATIONS see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism) due to risk of respiratory depression in the infant. There is no data available on the use of Prodeine during lactation. If Prodeine is administered to a breastfeeding mother, alternative arrangements should be made for feeding the infant.

Paracetamol and codeine pass into breast milk. 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 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, Prodeine 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

The codeine in Prodeine may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairing the mental and or physical ability required for the performance of potentially dangerous tasks, in some people. Those affected should not drive or operate machinery or engage in activities which require them to be alert.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reports of adverse reactions with paracetamol are rare. Dyspepsia, nausea, sweating, erythema, urticaria, anaphylactic shock, angioneurotic oedema, difficulty in breathing, skin rashes, drop in blood pressure, allergic and haematological reactions (thrombocytopenia, leukopenia, neutropenia, anaemia, agranulocytosis & pancytopenia) have been reported. A causal relationship to the administration of paracetamol has not been confirmed. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

Bronchospasm may be triggered in patients having a tendency of analgesic asthma.

Constipation, dry mouth, nausea and vomiting, dizziness, hypotension and drowsiness may occur in association with codeine. Other side effects are rare, especially at dosage levels provided with Prodeine. These include cough suppression, respiratory depression, confusional state, seizure, headache, somnolence, fatigue, sedation, euphoria, dysphoria, skin rashes, pruritus, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions. Long term use also entails the risk of drug dependence.

Tinnitus and miosis have been associated with codeine use. Visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients.

Very rarely, skin rashes may occur in patients hypersensitive to codeine. Pancreatitis has been reported very rarely.

Renal failure, uraemia, urinary retention or hesitance have been reported less frequently to rarely when both paracetamol and codeine have been administered.

Haemolytic anaemia, particularly in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported.

Kounis syndrome has been reported, as has high anion gap metabolic acidosis due to pyroglutamic acidosis in patients with pre-disposing factors-(see section 4.4). Bronchospasm has also been reported.

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.

It has been reported that paracetamol may produce symptoms of acute toxicity in adults, following the ingestion of more than 15g. Hepatotoxicity may develop after the ingestion of a single dose of 10 to 15g (200 to 250 mg/kg) and a dose of more than 25g is potentially fatal. 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. Patients may be asymptomatic for several days following ingestion of large doses of paracetamol and laboratory evidence of hepatotoxicity may be delayed for up to one week. Non-fatal hepatic damage is usually reversible. The antidote, N-acetylcysteine, should be administered as early as possible.

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

Determinations of the plasma concentration of paracetamol are recommended.

Plasma concentration of paracetamol should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Where paracetamol intoxication is suspected, intravenous administration of SH group donors such as acetylcysteine within the first 10 hours after ingestion is indicated. Although acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case it is taken for longer.

In an evaluation of codeine intoxication in children, symptoms ranked by decreasing order of frequency included sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur. Blood concentrations of codeine ranged from 1.4 to 5.6 µg/mL in eight adults whose deaths were attributed primarily to codeine overdosage.

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.

Relating to codeine component:

In general, treatment 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 the opioid antagonist naloxone hydrochloride is an antidote to respiratory depression; naloxone 400 microgram may be administered SC, IM or IV.

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 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Paracetamol is an analgesic and antipyretic. It reduces fever by a direct effect on the heat-regulating centres to increase dissipation of body heat.

Codeine phosphate hemihydrate acts centrally on opiate receptors. Its analgesic effect is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Paracetamol is rapidly absorbed from the gastrointestinal tract with peak plasma levels usually reached half to one hour after oral administration. Food intake delays paracetamol absorption.

Codeine is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption.

Distribution

Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). A minor proportion (less than 20%) is metabolised to catechol derivatives, and mercapturic acid compounds via oxidation. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdose (more than 150 mg/kg or 10 mg total paracetamol ingested) and if left untreated can cause irreversible liver damage. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant.

Excretion

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 4 hours.

Codeine is metabolised in the liver to morphine and norcodeine, which with codeine, are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Prodeine also contains COMPAP L, sodium starch glycollate, purified talc and magnesium stearate.

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 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Prodeine is available in blister packs of 24 caplets.

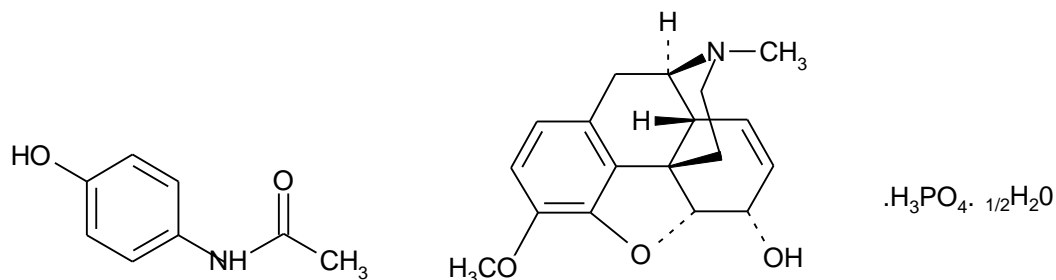
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Paracetamol is an odourless, crystalline powder or crystals with a bitter taste. Codeine phosphate hemihydrate is an odourless, crystalline powder or small colourless crystals with a bitter taste.

Chemical structure



paracetamol MW 151.17

codeine phosphate hemihydrate MW 406.37

CAS number

CAS - 103-90-2 (paracetamol). CAS 41444-62-6 (codeine phosphate hemihydrate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINE (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

4 September 2012

10 DATE OF REVISION

06 May 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Safety update to include the risk of high anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis.
4.5	Safety update to include the risk of HAGMA due to pyroglutamate acidosis
4.8	Safety update to include the risk of HAGMA due to pyroglutamate acidosis