AUSTRALIAN PRODUCT INFORMATION – MERSYNDOL FORTE (PARACETAMOL, CODEINE PHOSPHATE HEMIHYDRATE, DOXYLAMINE SUCCINATE)

1 NAME OF THE MEDICINE

Paracetamol, codeine phosphate hemihydrate and doxylamine succinate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 450 mg, codeine phosphate hemihydrate 30 mg, doxylamine succinate 5 mg.

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

3 PHARMACEUTICAL FORM

white tablets

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For relief of severe pain not responding to milder analgesics.

MERSYNDOL FORTE is suitable for individuals who cannot tolerate aspirin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years of age and older: One or two tablets every 4 to 6 hours as needed for relief. Do not exceed 8 tablets in a 24 - hour period. Mersyndol Forte is contraindicated for use in patients who are:

- 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. (See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric use)

4.3 CONTRAINDICATIONS

MERSYNDOL FORTE should not be given to patients with a known hypersensitivity to paracetamol, codeine, doxylamine succinate or any of the excipients listed under Section 6.1 LIST OF EXCIPIENTS.

It must not be used in patients with known glucose-6-phosphate-dehydrogenase deficiency or pre-existing respiratory depression, for example acute asthma, acute exacerbations of chronic obstructive pulmonary disease since codeine may exacerbate the condition.

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

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

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).

Mersyndol Forte is contraindicated during breast-feeding (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in lactation).

Mersyndol Forte is contraindicated for use in patients who are:

- 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 life-threatening adverse reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric use).

Mersyndol Forte is contraindicated for use in patients who are CYP 2D6 ultra-rapid metabolisers (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 Metabolism).

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. In view of the increased risk of hepatotoxicity, the benefit should be weighed against the risk when administering Mersyndol 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.

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. 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. There have been reports of kidney damage, disturbances in clotting mechanisms, metabolic acidosis, hypoglycaemia, agranulocytosis, thrombocytopenia, methaemoglobinaemia and myocardial necrosis.

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. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately paracetamol treatment and seek medical advice.

Paracetamol should be used with caution in patients with:

- chronic alcohol use including recent cessation of alcohol intake
- low glutathione reserves
- Gilbert's syndrome

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve e.g. in emphysema, kyphoscoliosis, hypoxia, hypercapnia or even severe obesity or cor pulmonale, or chronic obstructive pulmonary disease.

Codeine should be administered with caution in patients with impaired cardiac, hepatic or renal function, hypotension, benign prostatic hyperplasia, urethral stenosis, chronic colitis ulcerative, gall bladder conditions, multiple sclerosis, hypothyroidism, adrenocortical insufficiency (e.g. Addison's disease), shock, myxedema, 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
- vomiting

These 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.

Codeine should be used with caution in patients with a history of drug abuse.

Prolonged use of high doses of codeine may produce dependence and or addiction. Tolerance may also result following repeated administration.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence develop with prolonged use of high doses with withdrawal symptoms after sudden discontinuation of the drug. Cross-tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission).

Administration must be discontinued gradually after prolonged treatments.

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

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.

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

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

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). Mersyndol Forte should also be used with caution in patients who have had 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 structure or recent urinary tract surgery since codeine may cause urinary retention.

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

Patients with known analgesic intolerance or known bronchial asthma must only use Mersyndol Forte after having consulted a physician (hypersensitivity reactions including bronchospasm are possible).

Risks from Concomitant Use of Opioids and Benzodiazepines

Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Risks from Concomitant Use of Opioids and Alcohol

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CYP2D6 Metabolism

Mersyndol 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 or 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 decent, 3% in African Americans and 1%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations.

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

This medication may be dangerous when used in large amounts or for long periods.

Use in hepatic impairment

Mersyndol Forte should be administered with caution to patients with hepatic dysfunction, viral hepatitis, and to patients taking other drugs which affect the liver.

Use in renal impairment

Mersyndol Forte should be administered with caution to patients with renal dysfunction.

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 undesirable effects due to opioid-induced urinary retention and the respiratory effects of opioid analgesics. Dose reduction may be required.

Paediatric use

Mersyndol 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: Paracetamol may 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 slow down the excretion of chloramphenicol, entailing the risk of increased toxicity.

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

Anticholinergics: Concomitant use of codeine and anticholinergic agents 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.

Alcohol: Codeine may potentiate the effects of alcohol and increase the likelihood of paracetamol toxicity (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.

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.

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 may develop. Combination of Mersyndol Forte and zidovudine should be avoided.

Antiperistaltic antidiarrhoeals (including kaolin, pectin, loperamide): Concurrent use of these agents with codeine may increase the risk of severe constipation and CNS depression.

Tranquillisers, sedatives, 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.

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).

Monoamine Oxidase Inhibitors: Non-selective MAOI's intensify the effects of opioid drugs, which can cause anxiety, confusion and significant respiratory depression and other side effects of unpredictable severity. 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 2 weeks 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.

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 or other CNS depressants (including alcohol) concomitantly with Mersyndol Forte may experience additive CNS depression.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 5.3 PRECLINICAL SAFETY DATA.

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 those drugs found in Mersyndol Forte.

However, prolonged high-dose use of codeine prior to delivery may prolong codeine withdrawal symptoms in the neonate.

Regular use during pregnancy may cause physical dependence in the foetus, 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 Mersyndol 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). Mersyndol Forte 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

Mersyndol 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, 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, Mersyndol 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

Mersyndol 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. Patients treated with this medicine 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

*Hypersensitiv*e

Less frequent to rare – skin rashes and other allergic reactions, histamine release (hypotension, flushing of the face, tachycardia, breathlessness)

Gastrointestinal

Common – constipation, nausea, vomiting

*Neurologic*al

Common – drowsiness, dizziness

Less frequent to rare - euphoria, dysphoria. At higher doses codeine may cause respiratory depression.

Hepatic

Very rare - pancreatitis

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. Large doses may produce hepatotoxicity.

Prolonged administration of high doses may result in drug dependence.

Haemolytic anaemia, particularly 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, and 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.

The intake of too high a dose of paracetamol can lead to impairment of liver function due to necrosis of liver cells, and this condition may progress to hepatic coma and may be fatal. Independently of these liver lesions, kidney damage as a result of necrosis of the renal tubules has also been reported.

Symptoms and signs of poisoning

The early stage of acute poisoning is typically characterized by nausea, vomiting, anorexia, pallor, abdominal pain and sweating and general malaise. This is usually followed by a 24 to 48 hour period in which the patient feels better; the symptoms however do not disappear altogether. The following stage is characterized by rapid increase in the size of the liver; serum transaminases and bilirubin rise, prothrombin time increases abnormally; urine excretion decreases and a slight increase in nitrogenous substances may develop. 3 to 5 days after poisoning, the clinical features most typically encountered are commonly jaundice, fever, foetor hepaticus, abnormal bleeding tendency, hypoglycaemia, etc., as well as all stages of hepatic encephalopathy.

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.

Reactions associated with doxylamine succinate overdosage may vary from central nervous depression to stimulation. Stimulation is particularly likely in children. Atropine-like signs and symptoms - dry mouth; fixed, dilated pupils; flushing and gastrointestinal symptoms may also occur. Severe rhabdomyolysis after doxylamine succinate overdose has been reported in humans.

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 micrograms per mL in eight adults whose deaths were attributed 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.

Treatment of poisoning

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 and 500 mL iced mannitol 20% by mouth 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; 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.

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 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Codeine is a potent analgesic. Paracetamol is an analgesic and antipyretic. Doxylamine succinate has calmative and antinauseant properties which can be useful in relieving tension and nausea associated with pain.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Metabolism

Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

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

Other ingredients are purified talc, sodium starch glycollate and magnesium stearate.

6.2 INCOMPATIBILITIES

No data available.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

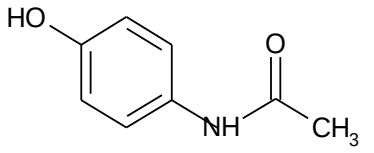
Blister packed white tablets in cartons of 20.

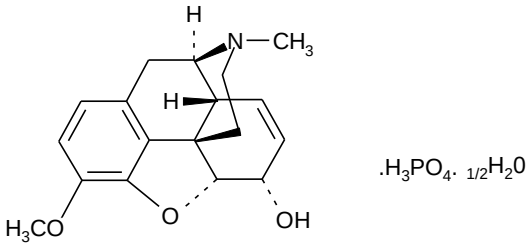
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

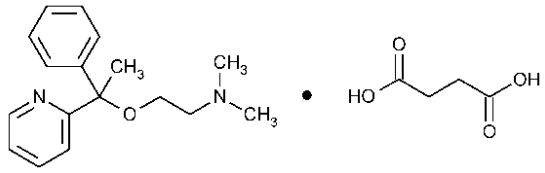
Chemical Structure





$.H_3PO_4 \cdot {}_{1/2}H_20$

Paracetamol Codeine phosphate hemihydrate



Doxylamine succinate

CAS number

Paracetamol: 103-90-2

Codeine phosphate hemihydrate: 41444-62-6

Doxylamine succinate: 562-10-7

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
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

8 July 1991

10 DATE OF REVISION

18 September 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	The PI reformatted in line with new template
4.4	Addition of a warning about codeine drug abuse
6.4	Add storage conditions
6.7	Add chemical structures and CAS numbers
8	Addition of contact details
4.4	Updated and added warnings in line with latest CCDSv3
4.7	Minor update to the wording to align with latest CCDSv3
4.8	Addition of 'particularly' for haemolytic anaemia to align with CCDSv3
4.9	Addition of overdose symptoms 'disseminated intravascular coagulation' to align with CCDSv3
4.5	Addition of interaction with CYP2D6 inhibitors and CYP3A4 inducers
4.4, 4.8	Addition of hypotension