Product Information

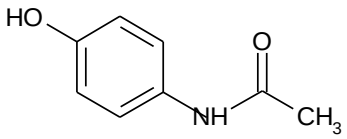
Prodeinextra

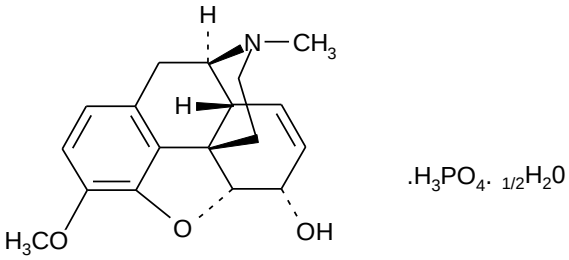
NAME OF THE MEDICINE

Non-proprietary Name

Paracetamol and codeine phosphate hemihydrate.

Chemical Structure





Paracetamol MW 151.17

Codeine phosphate hemihydrate MW 406.37

CAS Numbers

Paracetamol: CAS No. 103-90-2

Codeine Phosphate hemihydrate: CAS No. 1444-62-6

DESCRIPTION

Each capsule-shaped tablet (caplet) contains paracetamol 500 mg and codeine phosphate hemihydrate 15 mg and maize starch, purified talc, pregelatinised maize starch, povidone, stearic acid, potassium sorbate, magnesium stearate and microcrystalline cellulose.

PHARMACOLOGY

Analgesic and antipyretic.

Paracetamol's analgesic mechanism of action has not been fully elucidated but may involve blocking impulse generation at the bradykinin-sensitive chemoreceptors, that evoke pain. The antipyretic effect of paracetamol rises from its ability to block the action of prostaglandin synthetase and so prevent the synthesis of prostaglandins in response to the pyrogen stimulus in the region of the anterior hypothalamus.

Codeine acts centrally. It produces analgesia by dulling the response to painful stimuli at several loci in the CNS. This causes an alteration in the sensation and affective response of pain.

There is evidence to suggest that a combination of paracetamol with codeine is superior in analgesic action to either drug administered alone.

Pharmacokinetics

Absorption

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 minutes after administration. Food intake delays paracetamol absorption. Codeine has about one-sixth of morphine's analgesic activity. It 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. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant.

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

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.

CLINICAL TRIALS

No information available.

INDICATIONS

For patients over the age of 12 for the symptomatic relief of acute moderate to severe pain and fever, associated with strong headache, migraine pain, muscle pain, period pain, backache and toothache.

CONTRAINDICATIONS

Hypersensitivity to paracetamol or codeine or other ingredients.

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.

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

Prodeinextra is contraindicated during breast-feeding (see PRECAUTIONS).

Prodeinextra is not for use in children under 12 years of age.

Codeine should not be used in children aged below 18 years of age who have undergone tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory adverse reactions.

Codeine is also contraindicated in patients for whom it is known they are CYP 2D6 ultra-rapid metabolisers.

Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth.

PRECAUTIONS

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

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve eg in emphysema, kyphoscoliosis, hypoxia, hypercapnia or even severe obesity or cor pulmonale, or chronic obstructive pulmonary disease. Codeine may exacerbate respiratory impairment and CNS depression. Codeine should be administered with caution in patients with impaired cardiac, hepatic or renal function, and in cases of benign prostatic hyperplasia, urethral stenosis, chronic colitis ulcerative, gallbladder conditions, multiple sclerosis, hypothyroidism, adrenocortical insufficiency (eg Addisons'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 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.

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.

Codeine should only be used after careful risk-benefit assessment 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

Prodeinextra 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. Hence children engaging in bike riding and other hazardous activities should be supervised to avoid potential harm.

Adults should not drive, operate machinery, or drink alcohol whilst taking this medication.

Patients with known analgesic intolerance or known bronchial asthma must only use Prodeinextra after having consulted a physician (hypersensitivity reactions including bronchospasm 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
- severe renal insufficiency
- chronic alcohol use including recent cessation of alcohol intake
- low glutathione reserves
- Gilbert's syndrome

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). Prodeinextra 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.

Codeine should be administered with caution in patients taking Monoamine Oxidase Inhibitors (MAOIs) - see INTERACTIONS WITH OTHER MEDICINES.

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 therapeutic effect will not be obtained.

In ultra-rapid opiate/codeine metabolisers, there is an increased risk of developing opioid toxicity even at low doses. Symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Prevalence of CYP 2D6 ultrarapid metabolisers differs according to racial and ethnic group.

Codeine is not recommended for use in children in whom respiratory function might be compromised.

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 INTERACTIONS).

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine (see 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 INTERACTIONS).

Use in 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 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 Prodeinextra should be avoided during the third trimester of pregnancy and during labour.

Use in Lactation

Prodeinextra is contraindicated during breast-feeding (see CONTRAINDICATIONS). Paracetamol is excreted in breast milk but neither paracetamol nor its metabolites were detected in the urine of nursing infants after 650 mg maternal dose. If Prodeinextra is administered to a nursing mother, alternative arrangements should be made for feeding the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breast feeding 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 PRECAUTIONS).

Breast feeding patients 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

Paediatric Use

This medication is not suitable for children under 12 years of age.

Use in the Elderly

Elderly people may be more sensitive to the effects of this medicinal product, especially respiratory depression. 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.

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.

Effect 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.

INTERACTIONS WITH OTHER MEDICINES

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 antivitamin K. Patients should be monitored for appropriate coagulation and bleeding complications.

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

Diflusinal: 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. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

Propantheline: Decreases gastric emptying which may decrease the absorption of paracetamol.

Alcohol: Codeine may potentiate the effects of alcohol. 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 PRECAUTIONS).

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.

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. buphenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

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. 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 PRECAUTIONS).

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) barbiturates, rifampicin and alcohol.

Zidovudine: When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of Prodeinextra and zidovudine should be avoided. If chronic paracetamol and ziduvodine are to be given concurrently, monitor white blood cell 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 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 two 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 this codeine-containing medicine may exhibit additive CNS depression.

ADVERSE 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

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 (see PRECAUTIONS), cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

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

Codeine has also been associated with confusional state, dysphoriam, seizure, headache, somnolence, sedation, miosis, tinnitus, dry mouth, pruritus, fatigue. 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.

DOSAGE AND ADMINISTRATION

Adults and Children over 12 years

2 caplets every four to six hours as required (maximum 8 caplets in 24 hours).

OVERDOSAGE

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, 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 and 500 mL iced mannitol 20% by mouth may reduce absorption.

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 donators 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.

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 (Parvolex, David Bull) immediately without waiting for positive urine test or plasma level results: initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in 500 mL 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, 1g 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.

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; 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 Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

White to off-white capsule-shaped tablets (caplets) marked “PRO 15” and scored on one side with a plain reverse.

Available in blister packs of 6*, 12*, 20*, 24 and 40 caplets. Store below 30°C.

* Denotes presentations not available in Australia.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty limited
12-24 Talavera Road
Macquarie Park NSW 2113
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

Pharmacist Only Medicine (Schedule 3).

DATE OF FIRST INCLUSION IN THE ARTG

4 February 2013

DATE OF MOST RECENT AMENDMENT

21 April 2017

* Changes of clinical significance