

# PRODUCT INFORMATION

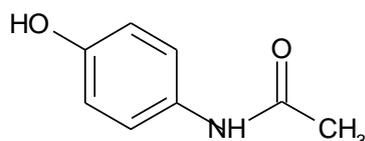
## PANADEINE FORTE

### NAME OF THE MEDICINE

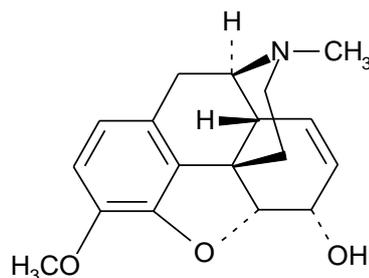
#### Australian Approved Name

Paracetamol and codeine phosphate

#### Chemical Structure



Paracetamol MW 151.17



.H<sub>3</sub>PO<sub>4</sub> · 1/2 H<sub>2</sub>O

Codeine phosphate MW 406.37

#### CAS Numbers

Paracetamol: CAS No. 103-90-2

Codeine phosphate hemihydrate: CAS No. 41444-62-6

#### Chemical Formula

Paracetamol: C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>

Codeine phosphate: C<sub>18</sub>H<sub>24</sub>NO<sub>7</sub>P, 1/2 H<sub>2</sub>O

#### Chemical Name

Paracetamol: N-(4-Hydroxyphenyl)acetamide

Codeine phosphate: 7,8-Didehydro-4,5 $\alpha$ -epoxy-3-methoxy-17-methylmorphinan-6 $\alpha$ -ol phosphate hemihydrate

### DESCRIPTION

Each capsule-shaped tablet contains Paracetamol 500 mg, Codeine phosphate 30 mg.

Other ingredients are maize starch, povidone, potassium sorbate, microcrystalline cellulose, stearic acid, magnesium stearate, purified talc, pregelatinised maize starch, and croscarmellose sodium.

Paracetamol is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. It has a melting point between 168°C and 172°C.

Codeine phosphate is a white or almost white, crystalline powder or small, colourless crystals. It is freely soluble in water and slightly soluble or very slightly soluble in ethanol (96 per cent).

### PHARMACOLOGY

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

## **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.

Codeine is metabolised in the liver to morphine and norcodeine.

## **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, morphine and norcodeine are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours.

## **INDICATIONS**

Relief of moderate to severe pain, and fever.

## **CONTRAINDICATIONS**

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

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.

Panadeine Forte is contraindicated during breast-feeding (see PRECAUTIONS).

## **PRECAUTIONS**

Panadeine Forte 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 Panadeine 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.

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.

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 should be administered with caution in patients with hypothyroidism, adrenocortical insufficiency (eg 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 and vomiting which are important signs in following the clinical course of patients with head injuries.

Codeine should be used with caution in patients with a history of drug abuse. Prolonged use of high doses of codeine may produce dependence. Tolerance may also result following repeated administration.

Panadeine Forte may cause drowsiness 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 Panadeine Forte after having consulted a physician (hypersensitivity reactions including bronchospasm possible).

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). Panadeine Forte should also be used with caution in patients who have had recent gastrointestinal tract surgery.

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.

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.

## **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 Panadeine Forte should be avoided during the third trimester of pregnancy and during labour.

## **Use in Lactation**

Panadeine Forte 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 Panadeine Forte 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**

Panadeine Forte can be given in reduced doses to children over the age of 7 years (see Dosage and Administration). This medication is not suitable for children under 7 years of age.

## **Use in the Elderly**

The elderly are more likely to have age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

## **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.

## **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 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.

**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).

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

**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.

**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.

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

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

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

**Monoamine Oxidase Inhibitors:** Non-selective MAOI's intensify the effects of opioid drugs, which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAOI's or within 10 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAOI's (Reversible Inhibitors of Monoamine Oxidase A) and codeine, caution is advised with this drug combination.

**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.

## 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 and 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.

## DOSAGE AND ADMINISTRATION

### *Adults*

The initial dose is 1 tablet, repeated every 4 to 6 hours if necessary for mild to moderate pain. The initial dose is 2 tablets repeated every 4 to 6 hours if necessary (maximum 8 tablets per day) for severe pain.

### *Children 7 to 12 years*

The initial dose is 1/2 a tablet, repeated every 4 to 6 hours if required (maximum 3 tablets per day).

Tablets to be taken with water.

## **OVERDOSAGE**

### **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, 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.

### **Treatment**

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.

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 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. 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

## **PRESENTATION AND STORAGE CONDITIONS**

Panadeine Forte is available as capsule-shaped tablets containing 500mg paracetamol and 30mg codeine phosphate.

The capsule-shaped tablets are white to off-white, marked "P" and "F" either side of a scoreline on one side and plain on the other. The dimensions of the capsule-shaped tablet are 17.46 x 7.14 x 6.05mm.

Panadeine Forte is available in cartons of 2<sup>†</sup>, 4<sup>†</sup>, 10<sup>†</sup>, 20 and 50 capsule-shaped tablets packaged in PVC/Aluminium foil blisters. Store below 25°C.

<sup>†</sup> Denotes presentations not available in Australia.

## **NAME AND ADDRESS OF THE SPONSOR**

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

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (Schedule 4)

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

21 March 2000

## **DATE OF MOST RECENT AMENDMENT**

16 May 2014

\* Changes of clinical significance

