Codapane Forte
Paracetamol and codeine phosphate

PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredients: Paracetamol and codeine phosphate

Structural formulae:

Paracetamol
Molecular weight: 151.17
CAS Registry No.: 103-90-2

Codeine phosphate hemihydrate
Molecular weight: 406.37
CAS Registry No.: 41444-62-6

DESCRIPTION

Paracetamol is a white crystalline powder, sparingly soluble in water, freely soluble in alcohol, very slightly soluble in ether and in methylene chloride. Codeine phosphate hemihydrate appears as white, crystalline powder or small colourless crystals, freely soluble in water, slightly soluble in alcohol, practically insoluble in ether.

Codapane Forte tablets contain 500 mg of paracetamol (present as “Compap L”) and 30 mg of codeine phosphate as the active ingredients. Codapane Forte tablets also contain the following inactive ingredients: crospovidone, colloidal anhydrous silica, sodium lauryl sulfate, stearic acid and magnesium stearate.

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.
Pharmacokinetics

Paracetamol

Absorption. After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 15 to 75 minutes after administration. These results are not significantly different to those of Panadeine® Forte. Food intake delays 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.

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

Codeine has about one-sixth of the analgesic activity of morphine. It is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption.

It is metabolised in the liver to morphine and norcodeine. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

Codeine and its metabolites 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

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

- Codapane Forte 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 (COPD) since codeine may exacerbate the condition.
• Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion predisposes patients to paracetamol hepatotoxicity.

• Paracetamol should not be used in patients with a history of intolerance 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.

**PRECAUTIONS**

Codapane Forte should be given with care to patients with impaired renal or hepatic function, viral hepatitis, and to patients taking other drugs which affect the liver. In view of the increased risk of hepatotoxicity, the benefit should be weighed against the risk when administering Codapane 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.

Depending on the genetic variability of CYP2D6, the individual metabolising capacity for codeine may vary. Even therapeutic doses can lead to increased formation of the active metabolite morphine resulting in clinical signs of morphine intoxication (see **OVERDOSAGE**).

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.

Codapane 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.

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 administered with great 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 (COPD).

Patients with known analgesic intolerance or known bronchial asthma must only use Codapane Forte after having consulted a physician (hypersensitivity reactions including bronchospasm possible).
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 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). Codapane 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 hypothyroidism, adrenocortical insufficiency (eg Addison’s disease), shock, myxoedema, acute alcohol intoxication or delirium tremens since codeine may exacerbate the symptoms or increase the risk of respiratory and/or CNS depression.

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

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

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

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

**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.

*Australian Pregnancy Categorisation Definition of Category A*: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

**Use in Lactation**

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.

Codeine does pass into breast milk so should be avoided in breastfeeding women. When Codapane 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.

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**

Codapane 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, Mutagenicity, Impairment of Fertility**

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

**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.

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

*Tranquilisers, 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.

*Alcohol:* Codeine may potentiate the effects of alcohol and the likelihood of paracetamol toxicity may be increased by its concomitant use.

*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.

*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.

*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.
Barbiturates and antiepileptic medications: The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol, barbiturates or anti epileptic drugs.

Coumarins: Repeated high doses of paracetamol increase the risk of bleeding in patients taking warfarin and other coumarin derivatives. Monitoring of coagulation and bleeding complications is required.

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

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

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

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

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

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.

Zidovudine: When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of Codapane 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.

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.
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, anaphylactic shock, angioneurotic oedema, leukopenia, agranulocytosis and pancytopenia. Bronchospasms may be triggered in patients having a tendency of analgesic asthma.
DOSAGE AND ADMINISTRATION

Tablets are to be taken with a glass of water.

Adults

*Mild to moderate pain*: The initial dose is 1 tablet, repeated every 4 to 6 hours if necessary.

*Severe pain*: The initial dose is 2 tablets, repeated every 4 to 6 hours if necessary (maximum of 8 tablets in 24 hours).

**Children 7 to 12 years**

The initial dose is half a tablet, repeated every 4 to 6 hours if required (maximum of 3 tablets in 24 hours).

OVERDOSAGE

**Symptoms**

Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma. 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 overdose, 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 50 mg/kg in 500 mL 5% glucose over 4 hours and 100 mg/kg in 1 L 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.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Codapane Forte tablets are white, oblong, convex tablets debossed with “PC/F” (“PC” over breakline over “F”) on one side and “α” on the other.

They are supplied in blister packs of 20s and 50s*.

*Not currently marketed in Australia

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

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DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

29 March 2005.

Date of most recent amendment: 29 March 2012.