PRODUCT INFORMATION
PANAMAX CO

NAME OF THE MEDICINE
Non-proprietary Name
Paracetamol and codeine phosphate

DESCRIPTION
Each tablet contains: Paracetamol 500 mg, codeine phosphate 8 mg.
Other ingredients are maize starch, povidone, potassium sorbate, microcrystalline cellulose, stearic acid, magnesium stearate, purified talc and pregelatinised maize starch
CAS - 103-90-2 (paracetamol). CAS 41444-62-6 (codeine phosphate hemihydrate)

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\begin{align*}
\text{paracetamol MW} & \quad 151.17 \\
\text{codeine phosphate MW} & \quad 406.37
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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
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 sulfate 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.

INDICATIONS
For patients over the age of 12 for the relief of acute moderate to severe pain, and fever.

CONTRAINDICATIONS
Panamax Co 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. Panamax Co is contraindicated during breast-feeding (see PRECAUTIONS). Panamax co should not be used in children (aged below 18 years) who undergo tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory adverse reactions. It is also contraindicated in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers. Panamax co is not recommended for use in children under 12 years old.

PRECAUTIONS
Panamax Co should be administered with caution to patients with hepatic or renal dysfunction. Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction.

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. Prolonged use of high doses of codeine may produce dependence.

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 Panamax Co after having consulted a physician (hypersensitivity reactions including bronchospasm possible).

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 ultra-rapid metabolisers differs according to racial and ethnic group.

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

**Use in Pregnancy**

Category A

There are no indications of a connection between the occurrences of malformations in newborn infants and the use of paracetamol within the recommended dose range during the first four months of pregnancy. During pregnancy, however, the patient is requested to use Panamax Co only after a thorough assessment of possible risks and benefits by the physician. 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 Panamax Co should be avoided during the third trimester of pregnancy and during labour.

**Use in Lactation**

Panamax Co is contraindicated during breast-feeding (see CONTRAINDICATIONS). Paracetamol and 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).

**INTERACTIONS WITH OTHER MEDICINES**

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Anticoagulant dosage may require reduction and patients should be monitored for appropriate coagulation and bleeding complications.

Paracetamol absorption is increased by drugs, which increase gastric emptying, eg. metoclopramide, and decreased by drugs, which decrease gastric emptying, eg. propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations. 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), hypnotics, rifampicin and alcohol.

When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Panamax Co and zidovudine should be avoided.

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. Concurrent administration of sedatives or tranquillisers may enhance the potential respiratory depressant effects of codeine.

**ADVERSE REACTIONS**

**Paracetamol**

Reports of adverse reactions are rare. Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted: dyspepsia, sweating, erythema, urticaria, anaphylactic shock, angioneurotic oedema, difficulty breathing, drop in blood pressure, nausea, allergic reactions such as skin rashes, and haematological reactions, including thrombocytopenia, leukopenia, neutropenia, agranulocytosis and pancytopenia. Bronchospasm 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) 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.

**Codeine**

Nausea and vomiting, constipation, dizziness and drowsiness have been reported at therapeutic doses. Very rarely, skin rashes may occur in patients hypersensitive to codeine. There have also been very rare reports of pancreatitis.

**DOSAGE AND ADMINISTRATION**

**Adults and children 12 years of age and older**

1 to 2 tablets (maximum 8 tablets per day).

To be taken with water; repeat every – 4 - 6 hours if necessary.

**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. Overdose 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 15g (30 tablets) of paracetamol; a dose of 25g (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.

**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. Gastric lavage is essential even if several hours have elapsed. Prompt administration of 50g activated charcoal and 500mL iced mannitol 20% by mouth may reduce absorption.

If the history suggests that 15g paracetamol or more has been ingested, administer one of the following antidotes:

*Acetylcysteine 20% i.v*

Administer 20% acetylcysteine (Parvorex, 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*

2.5g immediately followed by three further doses of 2.5g 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. 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
Tablets (white, scored, marked PANAMAX CO.), 40s

NAME AND ADDRESS OF SPONSOR
sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE
PHARMACIST ONLY MEDICINE (40s) (Schedule 3)

DATE OF FIRST INCLUSION IN THE ARTG
15 December 1997

DATE OF MOST RECENT AMENDMENT
30 October 2014

* Changes of clinical significance