PRODUCT INFORMATION
PANAMAX CO

NAME OF THE MEDICINE

Non-proprietary Name
Paracetamol and codeine phosphate hemihydrate

DESCRIPTION
Each tablet contains: Paracetamol 500 mg, codeine phosphate hemihydrate 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} & \quad \text{MW 151.17} \\
\text{codeine phosphate hemihydrate} & \quad \text{MW 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 gluconic acid. Excretion is almost complete within 24 hours.

INDICATIONS
For the relief of acute moderate pain.

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, patients with severe hepatocellular insufficiency, of pre-existing respiratory depression.

Panamax Co is contraindicated for use in patients who are:
- CYP2D6 ultra-rapid metabolisers (see PRECAUTIONS - CYP2D6 metabolism).
- younger than 12 years (see PRECAUTIONS – Paediatric Use).
- aged between 12 - 18 years in whom respiratory function might be compromised including post tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea, due to an increased risk of developing serious and life-threatening adverse reactions (see PRECAUTIONS – Paediatric Use).
- breast-feeding (see PRECAUTIONS–Use in Lactation).

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

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.

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. 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 must be administered with caution in certain patients such as those who present with impaired cardiac, hepatic or renal function, and in cases of benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison’s disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, gallbladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

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 used with caution in patients with convulsive disorders.

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, consumed in higher doses and over a prolonged period, may cause addiction.

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

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.

Panamax Co may cause drowsiness, disturbances of visuomotor coordination and visual acuity. 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).

**CYP2D6 metabolism**

Panamax Co 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 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 of respiratory depression to infants of rapid metaboliser mothers who take codeine. The prevalence of of codeine ultra-rapid metabolism by CYP 2D6 in children is not known, but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers differs according to racial and ethnic group. It is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations. (See also the sections on Paediatric Use and Use in Lactation.)

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

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. If Panamax Co is administered during pregnancy, morphinomimetic properties of codeine should be taken into account. 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 see also PRECAUTIONS-CYP2D6 metabolism) due to risk of respiratory depression in the infant. Paracetamol and codeine is excreted into human breast milk. Analgesic doses excreted in breast milk are generally low. However, infants of breastfeeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultrarapid 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– CYP2D6 metabolism).

Therefore, Panamax Co 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. Breastfeeding 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.

Paediatric Use
Panamax Co 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 PRECAUTIONS – CYP2D6 metabolism.)

Use in 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.

Effects on laboratory tests
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
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 or domperidone, 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

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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.

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.

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.

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with this codeine-containing drug may exhibit additive CNS depression.

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).

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).

A codeine-induced respiratory depression can be potentiated by tricyclic antidepressants.

Concomitant administration of Monoamine Oxidase Inhibitors (MAOIs) can potentiate the central nervous effects and other side effects of unpredictable severity. Codeine should not be used within two weeks after the discontinuation of MAOI treatment.

Concomitant use of codeine with antiperistaltic antidiarrhoeal drugs can increase the risk of severe constipation and CNS depression.

Morphininc agonists-antagonists – Concomitant use of codeine with a partial agonist (eg buprenorphine) or antagonist (eg naltrexone) can precipitate or delay codeine effects.

**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 edema, 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. Other adverse reactions reported to be associated with codeine include: confusional state, dysphoria, euphoria, seizure, headache, somnolence, fatigue, sedation, respiratory depression, dry mouth, pruritus, miosis, tinnitus and urinary
retention. Visuomotor coordination and visual acuity may be adverse affected in a dose-dependent manner at higher doses or in particularly sensitive patients. Long term use also entails the risk of drug dependence.

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.

Use in children under 12 years is contraindicated.

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 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.

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.

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.
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 (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 500mL 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.

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 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**

PRESCRIPTION ONLY MEDICINE (40s) (Schedule 4)

**DATE OF FIRST INCLUSION IN THE ARTG**

15 December 1997

**DATE OF MOST RECENT AMENDMENT**

26 September 2017

* Changes of clinical significance