PRODUCT INFORMATION
PANALGESIC

NAME OF THE MEDICINE

Non-proprietary Name
Paracetamol, codeine phosphate hemihydrate and doxylamine succinate

DESCRIPTION
Each capsule contains: Paracetamol 500 mg, codeine phosphate hemihydrate 8 mg, and doxylamine succinate 5 mg.

PHARMACOLOGY
Analgesic, antipyretic and calmative. There is evidence to suggest that a combination of paracetamol with codeine is superior in analgesic action to either drug administered alone. Doxylamine is an antihistamine with pronounced calmative effects.

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. 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. 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. 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.

Doxylamine has a half-life of approximately 9 hours.
INDICATIONS
For the relief of acute moderate pain.

CONTRAINDICATIONS
Panalgesic should not be administered to anyone hypersensitive to paracetamol, codeine, doxylamine or any of the excipients in used in this product. It must not be used in patients with known glucose-6-phosphate-dehydrogenase deficiency or pre-existing respiratory depression. Panalgesic must not be used in patients with impaired renal or liver function. It is also contraindicated 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 for obstructive sleep apnoea, due to an increased risk of developing serious and life-threatening adverse reactions (see PRECAUTIONS – Paediatric Use).
- breastfeeding (see PRECAUTIONS - Use in Lactation).
- Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth.

PRECAUTIONS
Panalgesic should not be administered to patients with hepatic or renal dysfunction (see CONTRAINDICATIONS). Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. This medication may be dangerous when used in large amounts or for long periods. Hepatotoxicity may develop following a dose of 10 g of paracetamol and hepatic failure is known to occur occasionally with the long term use of paracetamol.

To avoid the risk of overdose:
Check that paracetamol is absent from the composition of other medicinal products taken concomitantly.
Patients with known analgesic intolerance or known bronchial asthma must only use Panalgesic after having consulted a physician (hypersensitivity reactions including bronchospasm are 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:

- severe renal insufficiency
- chronic alcohol use including recent cessation of alcohol intake
- low glutathione reserves
- Gilbert's syndrome
Codeine should be used 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 CNS depression or decreased respiratory reserve eg emphysema, kyphoscoliosis, or 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.

Prolonged use of high doses of codeine may be habit-forming or produce dependence and or 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

Panalgesic may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairs the mental and or physical ability required for the performance of potentially dangerous tasks and a decrease in alertness. It should be used with caution in patients involved in tasks requiring complete alertness. If affected the patient should not drive a vehicle or operate machinery. Avoid alcohol.

**CYP2D6 metabolism**

Panalgesic 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 side effects of 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 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 ultrarapid 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 Panalgesic only after a thorough assessment of possible risks and benefits by the physician. If Panalgesic 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 Panalgesic should be avoided during the third trimester of pregnancy and during labour.
Use in Lactation

Panalgesic is contraindicated during breast-feeding (see CONTRAINDICATIONS, see also PRECAUTIONS-CYP2D6 metabolism) due to risk of respiratory depression in the infant. Paracetamol and codeine passes into the 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 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 also PRECAUTIONS - CYP2D6 metabolism).

Therefore, Panalgesic 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

Panalgesic 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 the Elderly

Elderly patients may be more sensitive to the effects of this medicinal product, especially respiratory depression. They are also more prone to suffering hypertrophy, prostatic obstruction and age-related renal impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.

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, e.g. metoclopramide or domperidone, and decreased by drugs which decrease gastric emptying, e.g. propantheline, anti-depressants with anti-cholinergic properties, narcotic analgesics.

Paracetamol may increase chloramphenicol concentrations by slowing down excretion, entailing the risk of increased toxicity. 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, hypnotics, rifampicin and alcohol.

When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Panalgesic 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 of 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.

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.

**ADVERSE REACTIONS**

**Paracetamol**

Reports of adverse reactions are rare. Although the following reactions have been reported: 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 and pancreatitis have been reported at therapeutic doses. Very rarely, skin reactions in patients hypersensitive to codeine. 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.

**Doxylamine**

Thickening of bronchial secretions, drowsiness.

**DOSAGE AND ADMINISTRATION**

**Adults and children over 12 years**

2 capsules every 4 hours as needed for relief. Not more than 8 capsules to be taken in 24 hours. Not recommended to be used for long periods.

Take with water.

**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**

It has been reported that paracetamol may produce symptoms of acute toxicity in adults, following the ingestion of more than 15g. 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.
In an evaluation of codeine intoxication in children, symptoms ranked by decreasing order of frequency included sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur. Blood concentrations of codeine ranged from 1.4 to 5.6 $\mu$g/mL in eight adults whose deaths were attributed primarily to codeine overdosage. 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.

Reactions associated with doxylamine overdosage may vary from CNS depression to stimulation. Stimulation is particularly likely in children; insomnia, nervousness, euphoria, irritability, tremors, nightmares, hallucinations and convulsions can occur. Atropine-like signs and symptoms such as dry mouth, fixed, dilated pupils, flushing and gastrointestinal symptoms may also occur.

**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.

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 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.

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

Capsules
white body with a yellow cap (marked ‘PANALGESIC’ on body and cap), 24s.

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

POISON SCHEDULE OF THE MEDICINE
Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG
10 September 1991

DATE OF MOST RECENT AMENDMENT
26 September 2017

* Changes of clinical significance