PRODUCT INFORMATION
MERSYNDOL FORTE TABLETS

NAME OF THE MEDICINE

Non-proprietary Name
Paracetamol, codeine phosphate and doxylamine succinate

DESCRIPTION
Each tablet contains paracetamol 450 mg, codeine phosphate 30 mg, doxylamine succinate 5 mg.
Other ingredients are talc – purified, sodium starch glycollate and magnesium stearate.

PHARMACOLOGY
Codeine is a potent analgesic. Paracetamol is an analgesic and antipyretic. Doxylamine succinate has calmative and antinauseant properties which can be useful in relieving tension and nausea associated with pain.
Metabolism: Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

INDICATIONS
For relief of severe pain not responding to milder analgesics.
MERSYNDOL FORTE is suitable for individuals who cannot tolerate aspirin.

CONTRAINDICATIONS
MERSYNDOL FORTE should not be given to patients with a known hypersensitivity to paracetamol, codeine, doxylamine succinate or any of the excipients listed under the Description.
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.

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

Mersyndol 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 Mersyndol 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.

It has been reported that paracetamol may produce symptoms of acute toxicity in adults following the ingestion of more than 15g.

Hepatotoxicity may develop after the ingestion of a single dose of 10 to 15g (200 to 250 mg/kg) and a dose of more than 25g is potentially fatal. Patients may be asymptomatic for several days following ingestion of large doses of paracetamol and laboratory evidence of hepatotoxicity may be delayed for up to one week. Non-fatal hepatic damage is usually reversible. There have been reports of kidney damage, disturbances in clotting mechanisms, metabolic acidosis, hypoglycaemia, agranulocytosis, thrombocytopenia, methaemoglobinemia and myocardial necrosis.

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
- vomiting

These 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.

Mersyndol Forte may cause drowsiness and/or dizziness.

Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion predisposes patients to paracetamol hepatotoxicity.

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). Mersyndol 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.

Patients with known analgesic intolerance or known bronchial asthma must only use Mersyndol Forte after having consulted a physician (hypersensitivity reactions including bronchospasm are 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.

Because doxylamine succinate may cause drowsiness in some patients, such patients should be cautioned about operating vehicles or machinery or engaging in activities which require them to be fully alert. Avoid alcohol.

This medication may be dangerous when used in large amounts or for long periods.

**Use in Pregnancy**

Category A. There have been no observations of an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus in pregnant women and women of child-bearing age who have taken those drugs found in Mersyndol Forte.

However, prolonged high-dose use of codeine prior to delivery may prolong codeine withdrawal symptoms in the neonate.

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 Mersyndol Forte should be avoided during the third trimester of pregnancy and during labour.

**Use in Lactation**

Mersyndol Forte is contraindicated during breast-feeding (see CONTRAINDICATIONS). There are no data available on the use of Mersyndol Forte during lactation. Paracetamol does pass into the breast milk. Neither paracetamol nor its metabolites were detected in the urine of nursing infants after 650 mg maternal dose.

Analgesic doses excreted in breast milk are generally low. However, 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.

**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:* 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.
*Diflusinal:* 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.
*Alcohol:* Codeine may potentiate the effects of alcohol and the likelihood of paracetamol toxicity may be increased by its concomitant use.
*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.
*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.
*Zidovudine:* When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Mersyndol Forte and zidovudine should be avoided.
*Antiperistaltic antidiarrhoicals (including kaolin, pectin, loperamide):* Concurrent use of these agents with codeine may increase the risk of severe constipation.
*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.
Monoamine Oxidase Inhibitors: Non-selective MAO I'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 MAO I's or within 10 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAOI I'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, anaphylactic shock, angioneurotic oedema, leukopenia 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. Large doses may produce hepatotoxicity. Prolonged administration of high doses may result in drug dependence.

DOSAGE AND ADMINISTRATION
Adults and children 12 years of age and older: One or two tablets every 4 to 6 hours as needed for relief. Do not exceed 8 tablets in a 24 - hour period. Not recommended for children under 12 years of age.

OVERDOSAGE
The intake of too high a dose of paracetamol can lead to impairment of liver function due to necrosis of liver cells, and this condition may progress to hepatic coma and may be fatal. Independently of these liver lesions, kidney damage as a result of necrosis of the renal tubules has also been reported.
**Symptoms and signs of poisoning**

The early stage of acute poisoning is typically characterized by nausea, vomiting, anorexia, pallor, abdominal pain and sweating and general malaise. This is usually followed by a 24 to 48 hour period in which the patient feels better; the symptoms however do not disappear altogether. The following stage is characterized by rapid increase in the size of the liver; serum transaminases and bilirubin rise, prothrombin time increases abnormally; urine excretion decreases and a slight increase in nitrogenous substances may develop. 3 to 5 days after poisoning, the clinical features most typically encountered are commonly jaundice, fever, foetor hepaticus, abnormal bleeding tendency, hypoglycaemia, etc., as well as all stages of hepatic encephalopathy. Overdose with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, metabolic acidosis, encephalopathy, coma and death. It can also lead to pancreatitis and acute renal failure.

Reactions associated with doxylamine succinate overdosage may vary from central nervous depression to stimulation. Stimulation is particularly likely in children. Atropine-like signs and symptoms - dry mouth; fixed, dilated pupils; flushing and gastrointestinal symptoms may also occur. Severe rhabdomyolysis after doxylamine succinate overdose has been reported in humans.

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 micrograms per mL in eight adults whose deaths were attributed to codeine overdosage.

**Treatment of poisoning**

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 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**

Blister packed white tablets in cartons of 20.
NAME AND ADDRESS OF THE 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
8 July 1991

DATE OF MOST RECENT AMENDMENT
18 July 2012