PRODUCT INFORMATION
MERSYNDOL

NAME OF THE MEDICINE

Non-proprietary Name

Paracetamol, codeine phosphate hemihydrate and doxylamine succinate.

DESCRIPTION

Mersyndol contains paracetamol 450 mg, codeine phosphate hemihydrate 9.75 mg, doxylamine succinate 5 mg. Paracetamol is an odourless, crystalline powder or crystals with a bitter taste. Codeine phosphate hemihydrate is an odourless, crystalline powder or small colourless crystals with a bitter taste. Doxylamine succinate is a powder with a characteristic odour.

Mersyndol also contains sodium starch glycollate, purified talc, magnesium stearate, microcrystalline cellulose, quinoline yellow CI 47005 and sunset yellow FCF 15985.

Mersyndol is aspirin-free.

PHARMACOLOGY

Paracetamol is an effective and fast-acting analgesic which relieves mild to moderate pain. It is rapidly absorbed from the gastrointestinal tract with peak plasma levels usually reached half to one hour after oral administration. It also reduces fever by a direct effect on the heat-regulating centres to increase dissipation of body heat.

Codeine phosphate hemihydrate is an effective oral analgesic which provides relief from mild to moderate pain. It is also well absorbed from the gastrointestinal tract after oral administration. The abuse potential of codeine is lower than that of other opiates.

Doxylamine succinate belongs to the ethanolamine class of antihistamines with sedative properties. Its calmative effect is useful in enhancing the effects of analgesics.

INDICATIONS

For patients over the age of 12 for the symptomatic relief of acute moderate to severe pain including headache, toothache, backache or pain associated with trauma or surgery.

The calmative properties of Mersyndol may be especially useful in the treatment of tension headache, migraine and period pain and the antipyretic properties may be useful in controlling fever.

CONTRAINDICATIONS

Known hypersensitivity to paracetamol, codeine or doxylamine succinate; patients with pre-existing respiratory depression. Patients with severe hepatocellular insufficiency. Patients with glucose-6-phosphate-dehydrogenase deficiency. Mersyndol is contraindicated during breast-feeding (see PRECAUTIONS). Mersyndol 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. Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth.

PRECAUTIONS

Mersyndol should be used with caution in severe hepatic or renal dysfunction. Hepatotoxcity 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.

Both doxylamine succinate and codeine may cause drowsiness in some patients. Codeine may also cause disturbances of visuomotor coordination and visual acuity, impairing the mental and or physical ability required for the performance of potentially dangerous tasks, thus patients should be cautioned about operating vehicles or machinery or engaging in activities which require them to be fully alert. Avoid alcohol.

Products containing codeine should not be given for prolonged periods as they may be habit-forming.

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.

Patients with known analgesic intolerance or known bronchial asthma must only use Mersyndol 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. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately paracetamol treatment 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 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 therapeutic effect will not be obtained.
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 ultrarapid metabolisers differs according to racial and ethnic group.
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 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. 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 should be avoided during the third trimester of pregnancy and during labour. Mersyndol should only be used during pregnancy under medical supervision if the potential benefit justifies the potential risk to the foetus. If administered during pregnancy, morphinomimetic properties of codeine should be taken into account.

Use in Lactation

Mersyndol is contraindicated during breast-feeding (see CONTRAINDICATIONS). There are no data available on the use of Mersyndol during lactation. 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).

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

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety or other CNS depressants eg. hypnotics, sedatives, tranquillisers, including alcohol, concomitantly may exhibit an 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).

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.

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

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 (eg buphenorphine) or antagonist (eg naltrexone) can precipitate or delay codeine effects.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as barbiturates and other antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol.

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

Paracetamol may considerably slow down the excretion of chloramphenicol, entailing the risk of increased toxicity. When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Mersyndol and zidovudine should be avoided.

Concurrent intake of drugs, which delay gastric emptying, such as propantheline, may slow down the uptake of paracetamol, thereby retarding its onset of action. Conversely, drugs, which accelerate gastric emptying, such as metoclopramide or domperidone, may accelerate the uptake of paracetamol and its onset of action.

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.

ADVERSE EFFECTS

Side-effects with Mersyndol are infrequent. However, among those reported are: anorexia, drowsiness, depression, dizziness, sweating, anaphylactic shock, angioneurotic oedema, difficulty in breathing, drop in blood pressure, gastrointestinal discomfort such as nausea and diarrhoea, dry mouth and, on rare occasions, erythema, urticaria, rash.

Paracetamol may occasionally cause skin reactions and isolated cases of agranulocytosis and thrombocytopaenic purpura have been reported. Changes in blood picture (rarely thrombocytopenia, neutropenia, leukopenia, and, in isolated cases, pancytopenia) may occur.

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 and cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

Doxylamine succinate may cause drowsiness in some individuals. Constipation and pancreatitis may occur in association with codeine.

Haemolytic anaemia in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported. Kounis syndrome and bronchospasm have also been reported.

Adverse effects reported relating specifically to the codeine component are: confusional state, dysphoria, euphoria, seizure, headache, somnolence, dizziness, sedation, miosis, tinnitus, respiratory depression, constipation, vomiting, nausea, dry mouth, pruritus, urinary retention and fatigue. Long term use also entails the risk of drug dependence. Visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients.

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 24-hour period. Not recommended to be used for long periods.

Children under 12 years

Not recommended.

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.

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. 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 deshydrogenase 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. 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. The antidote, N-acetylcysteine, should be administered as early as possible.

Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.
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 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 μg/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.
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.
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.

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

Mersyndol is available as tablets or caplets, each containing paracetamol 450 mg, codeine phosphate hemihydrate 9.75 mg and doxylamine succinate 5 mg.

The tablets are yellow, marked with 'M' inside two concentric circles on one side and 'Mersyndol 008' and a breakline on the reverse. Mersyndol is available in packs of 20 and 40 tablets.

The caplets are yellow, capsule-shaped tablets with 'Mersyndol' on one side and a breakline on the other. Mersyndol Caplets is available in packs of 20 and 40 caplets.

Storage Conditions: store below 30^{o}C

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Pharmacist Only Medicine (Schedule 3)

DATE OF FIRST INCLUSION IN THE ARTG

8 July 1991

DATE OF MOST RECENT AMENDMENT

21 April 2017

* Changes of clinical significance