AUSTRALIAN PRODUCT INFORMATION – MERSYNDOL DAYSTRENGTH (PARACETAMOL, CODEINE PHOSPHATE HEMIHYDRATE) UNCOATED TABLET

1 NAME OF THE MEDICINE

Paracetamol, codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mersyndol DayStrength contains paracetamol 500 mg and codeine phosphate hemihydrate 9.6 mg.

Mersyndol DayStrength is aspirin-free.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The caplets are yellow, capsule-shaped tablets with ‘Mersyndol’ on one side and ‘DS’ and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the relief of acute moderate pain and fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years of age and older:

One or two caplets every 3 to 4 hours as needed for relief. Do not exceed 8 caplets in 24-hour period.

Mersyndol DayStrength is not recommended for use over extended periods of time.

Use in children under 12 years is contraindicated.

4.3 CONTRAINDICATIONS

Mersyndol DayStrength is contraindicated in patients:

- with known hypersensitivity to paracetamol, codeine or any of the excipients used in this product.
- with pre-existing respiratory depression.
- with glucose-6-phosphate-dehydrogenase deficiency.
- with severely impaired liver or renal function.
- with diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).
- with chronic constipation.
- with active alcoholism.
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in neonate.
- during breast-feeding (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in lactation)
- 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use).
- who are CYP 2D6 ultra-rapid metabolisers (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - CYP2D6 metabolism).
- with acute asthma attack.

Mersyndol DayStrength is contraindicated for use in patients younger than 12 years (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in hepatic impairment)
- severe renal insufficiency (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in renal impairment)
- chronic alcohol use including recent cessation of alcohol intake
- low glutathione reserves
- Gilbert's syndrome

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve e.g. emphysema, kyphoscoliosis, or severe obesity.

Codeine should be administered with caution in patients with impaired cardiac, hepatic or renal function, urethral stenosis, gallbladder conditions, multiple sclerosis, hypothyroidism, adrenocortical insufficiency, shock, acute alcohol intoxication or prostatic hyperplasia, hypotension, myasthenia gravis, inflammatory or obstructive bowel disorders, recent gastrointestinal tract surgery, raised intracranial pressure or head injury.

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 dose of codeine may 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.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

Codeine should only be used after careful risk-benefit assessment in case of:

- Opioid dependence
- 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

Products containing codeine should not be taken in large amounts for prolonged periods as they may be habit-forming and should be used with caution in patients with a history of drug abuse.

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

CYP2D6 metabolism

Mersyndol DayStrength 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 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use and Section 4.6 FERTILITY, PREGNANCY AND LACTATION - 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in hepatic impairment

Mersyndol DayStrength should be used with caution in hepatic dysfunction.

Use in renal impairment

Mersyndol DayStrength should be used with caution in renal dysfunction.

Use in the elderly

Dosage should be reduced in elderly or debilitated patients because of the danger of respiratory or cardiac depression. Elderly people 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.

Paediatric use

Mersyndol DayStrength 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism).

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety or other CNS depressants e.g. hypnotics, sedatives, tranquillisers, including alcohol, concomitantly may exhibit an additive CNS depression. Concurrent use of codeine and other opioid analgesics is usually inappropriate as additive CNS depression, respiratory depression and other hypotensive effects may occur.

Morphinic agonists-antagonists: Concomitant use of codeine with a partial agonist (e.g. buprenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concurrent administration or use within 14 days of ceasing monoamine oxidase inhibitors (MAOIs) may enhance the potential respiratory depressant effects of codeine and other side effects of unpredictable severity.

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

Codeine may increase the hypotensive effects of antihypertensive agents.

Other potential interactions with codeine include anticholinergic agents or antidiarrhoeal agents (due to the risk of severe constipation and CNS depression); metoclopramide (as codeine may antagonise the effects of this medicine on gastrointestinal motility); and drugs that can inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents as they can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.

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 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 DayStrength 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 absorption rate of paracetamol and its onset of action.

Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol. Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy – 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 the active ingredients in Mersyndol DayStrength. However, prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate. Opioid analgesics 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 DayStrength should be avoided during the third trimester of pregnancy and during labour. Mersyndol DayStrength 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 DayStrength is contraindicated during breast-feeding (see Section 4.3 CONTRAINDICATIONS see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE -CYP2D6 metabolism) due to risk of respiratory depression in the infant. There is no data available on the use of Mersyndol DayStrength during lactation. If Mersyndol DayStrength is administered to a breastfeeding mother, alternative arrangements should be made for feeding the infant.

Paracetamol and codeine pass into 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 ultra rapid 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism).

Therefore, Mersyndol DayStrength 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The codeine in Mersyndol DayStrength may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairing the mental and or physical ability required for the performance of potentially dangerous tasks, in some people. Those affected should not drive or operate machinery or engage in activities which require them to be alert.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reports of adverse reactions with paracetamol are rare. Dyspepsia, nausea, sweating, anaphylactic shock, angioneurotic oedema, difficulty in breathing, erythema, urticaria, skin rashes, drop in blood pressure, allergic and haematological reactions (thrombocytopenia, neutropenia, leukopenia, anaemia, agranulocytosis & pancytopenia) have been reported. A causal relationship to the administration of paracetamol has not been confirmed. 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.

Bronchospasm may be triggered in patients having a tendency of analgesic asthma.

Constipation, dry mouth, nausea and vomiting, dizziness and drowsiness may occur in association with codeine. Other side effects are rare, especially at dosage levels provided with Mersyndol DayStrength. These include cough suppression, respiratory depression, confusional state, seizure, headache, somnolence, fatigue, sedation, euphoria, dysphoria, skin rashes, pruritis, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions. Long term use also entails the risk of drug dependence.

Tinnitus and miosis have been associated with codeine use. Visuomotor coordination and visual acuity may be adverse affected in a dose-dependent manner at higher doses or in particularly sensitive patients.

Very rarely, skin rashes may occur in patients hypersensitive to codeine. Pancreatitis has been reported very rarely.

Renal failure, uraemia, urinary retention or hesitance have been reported less frequently to rarely when both paracetamol and codeine have been administered.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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, disseminated intravascular coagulation, 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. 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.

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage (more than 150 mg/kg or 10 mg total paracetamol ingested) and if left untreated can cause irreversible liver damage. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant.

Excretion

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate 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. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite. The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mersyndol DayStrength also contains COMPAP L, sodium starch glycollate, purified talc, magnesium stearate and quinoline yellow (CI 47005).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

Mersyndol DayStrength is available as caplets of 24, 36, or 40, each containing paracetamol 500mg and codeine phosphate hemihydrate 9.6 mg.

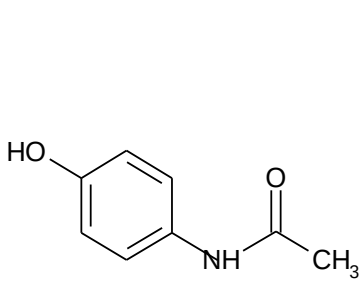
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

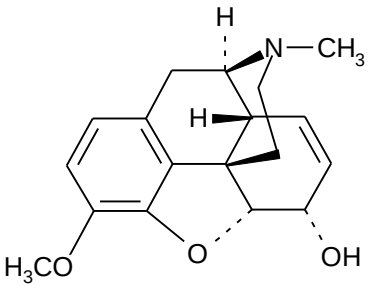
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical structure





$.H_3PO_4 \cdot {}_{1/2}H_20$

paracetamol MW 151.17 codeine phosphate hemihydrate MW 406.37

CAS number

CAS - 103-90-2 (paracetamol). CAS 41444-62-6 (codeine phosphate hemihydrate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINE (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

3 June 1997

10 DATE OF REVISION

2 August 2019

* Changes of clinical significance

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	The PI reformatted in line with new template
4.4	Minor Editorial Changes. Addition of a warning about codeine drug abuse.
6.1	Minor Editorial Changes
8	Addition of contact details
4.3	Addition of contraindications to align with CCDSv3
4.5	'uptake' has been reworded to 'absorption rate' for better clarity and to align with CCDSv3
4.8	Addition of 'particularly' for haemolytic anaemia to align with CCDSv3
4.9	Addition of overdose symptoms 'disseminated intravascular coagulation' to align with CCDSv3