

NEW ZEALAND DATA SHEET

1 MERSYNDOL

Mersyndol, 450 mg/9.75 mg/5 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mersyndol Tablets: Paracetamol 450 mg per tablet; Codeine Phosphate Hemihydrate 9.75 mg per tablet; Doxylamine Succinate 5 mg per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Mersyndol Tablets are yellow, round, flat faced bevelled edged tablets with a diameter of 12.7mm. One face is marked "M" within two concentric circles, the other "MERSYNDOL 008" and has a breakline.

4 CLINICAL PARTICULARS

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

Mersyndol is a suitable alternative for those individuals who cannot tolerate aspirin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Mersyndol Tablets

Adults, children 12 years and older: 1 or 2 tablets every four to six hours as needed for relief.

Do not exceed 8 tablets in a 24 hour period.

Not recommended for children under 12 years.

4.3 CONTRAINDICATION

- Known hypersensitivity to paracetamol, codeine, doxylamine succinate, other opioids or any excipients of Mersyndol Tablets
- Concomitant treatment with Monoamine inhibitors (MAOIs) or treatment within 14 days of stopping MAOIs (see Section 4.5 Interaction with other medicines and other forms of interaction)
- Severe hepatocellular insufficiency
- Pre-existing or acute respiratory depression
- Respiratory insufficiency
- Obstructive airways disease
- Acute asthma attack
- Patients with known glucose-6-phosphate-dehydrogenase deficiency
- Patients with known analgesic intolerance
- Patients with impaired liver function
- Acute alcoholism
- Head injuries or conditions in which intracranial pressure is raised. Codeine can increase the pressure of the 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.
- Patients at risk of paralytic ileus
- Breast-feeding mothers (see section 4.6)
- Children aged less than 12 years for all indications.
- 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 effects.
- Adolescents aged less than 18 years for pain following surgery to remove tonsils and adenoids
- Adolescents aged less than 18 years for symptomatic treatment of cough and cold
- Adolescents aged less than 18 years in whom respiratory function might be compromised.
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- In the event of impending childbirth or in the case of risk of premature birth.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mersyndol should be used with caution in patients with the following conditions:

- Hypothyroidism
- Adrenocortical insufficiency e.g. Addison's Disease
- Impaired kidney / liver function
- Prostatic hypertrophy
- Shock / hypotension
- Myasthenia gravis
- Convulsions / convulsive disorder
- Gall bladder disease or gall stones
- Recent gastro-intestinal surgery
- Urinary tract surgery
- Reduced respiratory function or history of asthma
- Obstructive and inflammatory bowel disease - codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping their treatment

Toxicity and Hepatotoxicity - 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 ingestion of a single dose of 10 to 15 g (200 to 250 mg/kg) and a dose of more than 25g is potentially fatal. Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. 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, methaemoglobinaemia and myocardial necrosis.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol should be used with caution in patients with severe hepatic or renal dysfunction (see section 4.3).

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 the following pre-disposing factors:

- Mild to moderate hepatocellular insufficiency
- Severe renal insufficiency and sepsis
- Chronic alcohol use including recent cessation of alcohol intake
- Malnutrition and other sources of low glutathione reserves
- Glucose-6-phosphate-dehydrogenase deficiency
- Gilbert's syndrome

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness and/or pre-disposing factors (see above) who were treated with paracetamol at therapeutic dose for a prolonged period or combination of paracetamol and flucloxacillin. Symptoms of HAGMA may include serious breathing difficulties with deep rapid breathing, drowsiness, nausea and vomiting. Prompt discontinuation of paracetamol and close monitoring is recommended if symptoms of HAGMA appear. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as the underlying cause of HAGMA in patients with multiple risk factors.

To avoid the risk of overdose: Check that paracetamol is absent from the composition of other medicinal products taken concomitantly.

Dependence - This medication may be dangerous when used in large amounts or for long periods and may cause addiction. Codeine phosphate hemihydrate may occasionally cause constipation. Codeine may be habit forming or produce 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 opioid dependence (including those in remission). Administration must be discontinued gradually after prolonged treatments. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for 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.

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.

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

- Opioid dependence
- Chronic constipation
- Impaired consciousness
- Compromised respiratory function (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airways disease

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.

Use with caution in patients with convulsive disorders.

Monitoring after prolonged use should include blood count, liver function and renal function.

Codeine must be administered with caution in certain patients, such as those who present with impaired cardiac, hepatic or renal function, hypotension, 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.

Opioid-Induced Hyperalgesia (OIH) or Allodynia

OIH occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

Use of Codeine in children population and risk of respiratory depression

Codeine is not recommended in children 12 to 18 years of age with risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as obstructive sleep apnoea, obesity, and pulmonary disease.

Hypersensitivity - Maculopapular rash, fever, splenomegaly and lymphadenopathy have been seen as part of a codeine hypersensitivity reaction.

Withdrawal - Abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate, and blood pressure. These effects can also occur in neonates exposed to codeine in utero (see section 4.6).

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Alcohol - Alcohol should be avoided. To avoid more serious adverse reactions, special caution must be exercised and intervals between doses must be increased and /or the dose reduced, when paracetamol is used in patients with chronic alcohol abuse. Use of codeine in patients with acute alcoholism is contraindicated.

Genetic polymorphism - Codeine is metabolised to morphine by cytochrome P450 2D6. Some patients are ultra-rapid metabolisers and are at higher risk of toxic opioid effects, 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 ultra-rapid metabolisers differs according to racial and ethnic group. Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

CYP2D6 metabolism – 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. Estimates indicate that up to 7% of the Caucasian population may have this deficiency.

Doxylamine must be administered with caution in patients with:

- urinary retention
- susceptibility to angle closure glaucoma

QT interval prolongation

Doxylamine may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, therefore caution is advised in patients concomitantly using another drug labeled for QT interval prolongation, and in patients with a risk factor for QT prolongation (e.g., hypokalemia), or in the overdose setting.

Risks from Concomitant Use of Opioids and Benzodiazepines

Profound sedation, respiratory depression, coma and death may result in the concomitant use of Mersyndol with benzodiazepines or other CNS depressants (e.g. non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilisers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol). Because of these risks, reserve concomitant prescribing of the drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see section 4.5).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on the clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of sedation and respiratory depression (see section 4.5).

Patients should be advised to first consult their healthcare professional before taking codeine if they are taking a benzodiazepine (see section 4.5).

Advise both patients and caregivers about the risks of respiratory depression and sedation when codeine is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate machinery until the effects of concomitant use of benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk of overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see section 4.5)

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).

Risk from concomitant use of opioids and gabapentinoids

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin) increases the risk of respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect. Concomitant use with gabapentinoids is not recommended.

Use in the Elderly

Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects of these medicines. Also geriatric patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment, and are therefore more likely to be adversely affected by opioid-induced urinary retention. The risk of constipation and faecal impaction is also greater in the elderly.

Geriatric patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective for these patients.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with Mersyndol should be considered.

Endocrine effects

Opioids, such as Mersyndol, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Hormonal disturbances that have been observed include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Neonatal Withdrawal Syndrome

Chronic use of codeine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth. (See section 4.6 - Use in Pregnancy).

Hepatobiliary disorders

Opioids may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, Mersyndol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Gastrointestinal Toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants such as anaesthetics, hypnotics, sedatives, tranquilizers and alcohol concomitantly with Mersyndol Tablets may exhibit an additive CNS depression. Concurrent administration of sedatives and tranquillisers may enhance the potential respiratory depressant effects of codeine.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacological effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4)
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilisers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol.

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).

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

Monoamine Oxidase Inhibitors (MAOI): Concomitant administration of MAOIs can potentiate the central nervous effects and other side effects of unpredictable severity, Mersyndol should not be used within 14 days after discontinuation of MAOI treatment.

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

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin) increases the risk of respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect.

Morphinic agonists-antagonists: Concomitant use of codeine with a partial agonist or antagonist 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 certain hypnotics,

antiepileptics (such as phenobarbital, phenytoin, carbamazepine and topiramate), rifampicin, barbiturates and alcohol. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Paracetamol may considerably slow down the excretion of chloramphenicol, resulting in toxicity.

Concurrent use of paracetamol and zidovudine increases the tendency for neutropenia to develop and should be avoided.

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.

When Mersyndol Tablets are taken after a meal, the onset of action may be delayed.

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

Co-administration of flucloxacillin with paracetamol may lead to high anion gap to metabolic acidosis due to pyroglutamic acidosis, particularly in patients with risk factors (see section 4.4).

CYP2D6 inhibitors: Codeine is metabolised by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers: Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

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.

Avoid concomitant use of codeine and:

- Monoamine Oxidase Inhibitors - due to the possible risk of excitation or depression, avoid concomitant use and for up to 14 days after discontinuation
- Alcohol – enhanced sedative and hypotensive effect, increased risk of respiratory depression

- Hypnotics and anxiolytics – enhanced sedative effect, increased risk of respiratory depression
- Anticholinergics - risk of severe constipation which may lead to paralytic ileus and/or urinary retention.
- Metoclopramide or domperidone - antagonistic effect on GI activity.
- Anti-diarrhoeal drugs - increased risk of severe constipation
- Anaesthetics - enhanced sedative and hypotensive effect.
- Tricyclic antidepressants – enhanced sedative effect
- Antipsychotics –enhanced sedative and hypotensive effect
- Opioid antagonists - may precipitate withdrawal symptoms.
- Quinidine - reduced analgesic effect
- Antihypertensive drugs - enhanced hypotensive effect.
- Ciprofloxacin - avoid premedication with opioids as they reduce ciprofloxacin concentration
- Ritonavir - may increase the plasma levels of opioid analgesics
- Mexiletine - delayed absorption of mexiletine
- Cimetidine - inhibits the metabolism of opioid analgesics causing increased plasma codeine concentrations

4.6 PREGNANCY AND LACTATION

Safe use in pregnancy has not been established in human studies; this medication should not be used in pregnancy unless in the opinion of the prescribing doctor the potential benefits outweigh the potential risks because opioid analgesics cross the placenta. If administered during pregnancy, morphinomimetic properties of codeine should be taken into account. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate. Codeine may cause respiratory depression and withdrawal syndrome in neonates born to mothers who use codeine during the third trimester of pregnancy. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Mersyndol during pregnancy. As a precautionary measure, use of Mersyndol should be avoided during the third trimester of pregnancy and during labor.

There is epidemiological evidence of safety in pregnancy for paracetamol and doxylamine succinate.

Although the embryo-toxicity/teratogenicity of doxylamine succinate has not been proven in humans, animal studies have demonstrated adverse effects on chondrogenesis.

Mersyndol Tablets are contraindicated during breast-feeding (see section 4.3). Codeine, doxylamine and paracetamol are excreted in breast milk.

Analgesic doses excreted in breast milk are generally low. However, infants of breast feeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Codeine is partially metabolised by cytochrome P450 2D6 (CYP 2D6) into morphine which is excreted into breast milk. Nursing mothers taking codeine who are CYP 2D6 ultra-rapid metabolisers may have higher morphine levels in their breast milk, which may lead to life-threatening or fatal side effects in nursing babies even at therapeutic doses.

If codeine has been taken, 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. Breastfed babies usually nurse every two to three hours and should not sleep more than four hours at a time. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice. Neither paracetamol nor its metabolites were detected in the urine of nursing infants after 650 mg maternal dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Both doxylamine succinate and codeine may cause drowsiness or a decrease in alertness in some patients. They may also cause disturbances of visuomotor coordination, visual acuity and psychomotor impairment impacting the mental and/or physical ability required for the performance of potentially dangerous tasks, such as operating vehicles or machinery, or engaging in activities which require them to be fully alert.

4.8 UNDESIRABLE EFFECTS

Side effects with Mersyndol Tablets are infrequent. However among those reported are fatigue, anorexia, drowsiness, depression, dizziness, gastrointestinal discomfort (nausea and diarrhoea), dry mouth and on rare occasions, redness of the skin or rash.

Hypersensitivity reactions such as, sweating, anaphylactic shock, angioneurotic oedema, angioedema, difficulty breathing and drop in blood pressure may occur.

Immune system disorders – erythema, rash, urticaria, pruritus, difficulty breathing, increased sweating, redness or flushed face, angioedema

Nervous system disorders – seizure, sedation, somnolence, confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness, excitement), convulsions, mental depression, headache, nightmares, raised intracranial pressure, tolerance or dependence, dysphoria, euphoria, hypothermia. Long term use also entails the risk of drug dependence.

Eye disorders - miosis, blurred or double vision. Visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients.

Ear and labyrinth disorders – Tinnitus

Cardiac disorders - bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia. Kounis syndrome has also been reported.

Respiratory, thoracic and mediastinal disorders - respiratory depression. Bronchospasm has also been reported.

Gastrointestinal disorders - constipation, biliary spasm, nausea, vomiting, dry mouth

Musculoskeletal, connective tissue and bone disorders - muscle rigidity

Renal and urinary disorders - ureteral spasm, anti-diuretic effect, urinary retention

Reproductive system and breast disorders - decrease in libido and potency

Metabolism and nutrition system disorders – High anion gap metabolic acidosis due to pyroglutamic acidosis, in patients with pre-disposing factors (see section 4.4).

Respiratory disorders with a frequency not known: Central sleep apnoea syndrome.

Hepatobiliary disorders with a frequency not known: Spasm of sphincter of Oddi.

Endocrine disorders with a frequency not known: Adrenal insufficiency and Androgen deficiency.

Withdrawal effects - abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate, and blood pressure. Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regular prolonged use of codeine is known to lead to addiction and tolerance. Prolonged use of a painkiller for headaches can make them worse.

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

Paracetamol may occasionally cause skin reactions. Isolated cases of agranulocytosis, neutropenia, thrombocytopenia and thrombocytopenic purpura have been reported with paracetamol. Changes in blood picture are possible (thrombocytopenia, leukopenia, agranulocytosis and pancytopenia). Haemolytic anaemia, particularly in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported. Toxic epidermal necrolysis

(TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption, cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

Prolonged or high dosage use may result in impaired liver or kidney function.

Doxylamine succinate may cause drowsiness or thickening of bronchial secretions in some individuals, as well as paradoxical stimulation, psychomotor impairment and blurred vision.

Very rarely, skin rashes may occur in patients hypersensitive to codeine. Very rarely, pancreatitis may occur.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions using the following website link:

<https://pophealth.my.site.com/carmreportnz/s/>.

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.

Symptoms

Toxic leukoencephalopathy has been observed with opioid overdose.

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.

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.

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 10-15g (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 1 week. Non-fatal hepatic damage is usually reversible.

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 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 donors such as N-acetylcysteine within the first 10 hours after ingestion is indicated. Although N-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 15 g paracetamol or more has been ingested, administer one of the following antidotes:

Acetylcysteine 20% iv: The antidote, N-acetylcysteine, should be administered as early as possible, 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 intensive care protocols.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Paracetamol is an effective and fast acting analgesic and antipyretic which acts centrally to relieve mild to moderate pain. Like the salicylates, paracetamol reduces fever by a direct action on the heat regulating centres to increase the dissipation of heat.

Codeine phosphate hemihydrate is an effective oral analgesic, which provides relief from mild to moderate pain. The abuse potential of codeine is lower than other opiates.

Doxylamine succinate belongs to the ethanolamine class of antihistamines with sedative properties.

5.2 PHARMACOKINETIC PROPERTIES

Paracetamol is rapidly and completely absorbed from the gastrointestinal tract after oral administration with peak plasma levels occurring 30 to 60 minutes after administration. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol.

The elimination half-life varies from about 1 to 4 hours.

The apparent volume of distribution is 1 to 1.2 L/kg. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increased concentrations. Paracetamol can cross the placenta and is excreted in milk. Food intake delays paracetamol absorption.

Codeine phosphate hemihydrate is well absorbed after oral administration. It is metabolised in the liver, mainly to the glucuronide conjugates, morphine (about 10%) and norcodeine (about 10%), which, with codeine, are excreted in the urine. Most of the excretion products appear in the urine within 6 hours and excretion of up to 86% of the dose is almost complete in 24 hours. The volume of distribution of codeine is 3.5L/kg and at therapeutic blood levels about 30% is protein bound.

Doxylamine succinate has an elimination half-life of approximately 9 hours

5.3 PRECLINICAL SAFETY DATA

There are no findings of relevance to the prescriber other than those mentioned elsewhere in this Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mersyndol Tablets:

Maize starch

Microcrystalline cellulose

Purified Talc

Sodium Starch Glycollate Magnesium Stearate

Quinoline yellow

Sunset yellow

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

Mersyndol Tablets:

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Mersyndol Tablets:

Blister packs of 20 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Mersyndol Tablets:
Prescription Only Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

Mersyndol Tablets:
31 March 1994

10 DATE OF REVISION OF THE TEXT

11 March 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of warning statements regarding doxylamine use and QT interval prolongation