

Data Sheet

Mersyndol®

Name of Medicine

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

Presentation

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.

Uses

Actions

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 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.

Pharmacokinetics

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 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.

Indications

Symptomatic relief of 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.

Dosage and Administration

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.

Contraindications

- Known hypersensitivity to paracetamol, codeine, doxylamine succinate, other opioids or any excipients of Mersyndol tablets
- Pre-existing or acute respiratory depression
- Obstructive airways disease
- Asthma
- 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
- Patients at risk of paralytic ileus

Warnings and Precautions

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 25 g 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, methaemoglobinaemia and myocardial necrosis.

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

Dependence - This medication may be dangerous when used in large amounts or for long periods. Codeine phosphate may occasionally cause constipation. Codeine may be habit forming or produce dependence. Codeine is not a satisfactory substitute for patients

dependent on morphine. Regular use of analgesics for headaches can result in an overuse syndrome.

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 USE IN PREGNANCY).

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. Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

Use in Pregnancy

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. 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.

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.

Use in Lactation

Both codeine and paracetamol are excreted in breast milk. Mersyndol should not be used during lactation without a thorough assessment of possible risks and benefits by a physician.

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. Nursing mothers taking codeine who are 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.

When prescribing codeine for a nursing mother, the lowest dose for the shortest amount of time to relieve pain or cough should be prescribed. 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.

Use in Children

Mersyndol should not be used in children under 12 years.

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.

Effects on Ability to Drive and Use Machines

Both doxylamine succinate and codeine may cause drowsiness or a decrease in alertness in some patients. Patients should be cautioned about operating vehicles or machinery, or engaging in activities which require them to be fully alert.

Adverse Effects

Side effects with Mersyndol are infrequent. However among those reported are 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, difficulty breathing and drop in blood pressure may occur.

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

Nervous system disorders - 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, hypothermia

Eye disorders - miosis, blurred or double vision

Cardiac disorders - bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia

Respiratory, thoracic and mediastinal disorders - respiratory depression

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

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.

Paracetamol may occasionally cause skin reactions. Isolated cases of agranulocytosis and thrombocytopenic purpura have been reported with paracetamol. Changes in blood picture are possible (thrombopenia, leucopenia, agranulocytosis and pancytopenia).

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.

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

Interactions

Patients receiving CNS depressants such as anaesthetics, hypnotics, sedatives, tranquilizers and alcohol concomitantly with Mersyndol may exhibit an additive CNS depression. Concurrent administration of sedatives and tranquillisers may enhance the potential respiratory depressant effects of codeine.

Barbiturates and prolonged alcohol ingestion may increase the metabolism of paracetamol to metabolites toxic to the liver.

Certain hypnotics, antiepileptics (Phenobarbital, phenytoin and carbamazepine) and rifampicin when administered concomitantly with paracetamol products may increase the metabolism of paracetamol which can result in liver damage.

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 coumarin derivatives, particularly if paracetamol is taken at high doses or for several days. Patients taking paracetamol and coumarin derivatives should be monitored for appropriate coagulation and bleeding complications.

When Mersyndol is 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 uptake of paracetamol, thereby retarding its onset of action. Conversely, drugs which accelerate gastric emptying, such as metoclopramide, may accelerate the uptake of paracetamol and its onset of action.

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

Overdosage

Symptoms

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.

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. 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

Consists primarily of management of paracetamol toxicity; naloxone is the treatment of choice for codeine intoxication. 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.

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.

Contact the National Poisons Information Centre for advice on management of overdose.

Pharmaceutical Precautions

Store below 30°C.

Shelf Life

24 months

Medicine Classification

Pharmacist Only Medicine

Package Quantities

In blister packs of 20 tablets

Further Information

Nil

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Date of Preparation

30 May 2011