

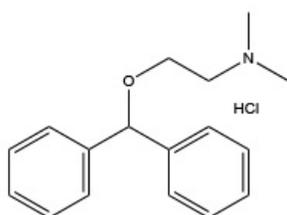
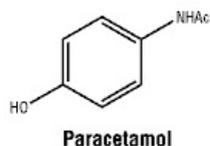
PRODUCT INFORMATION

MersynoNight™ Night Time Pain Relief

NAME OF THE MEDICINE

Non-proprietary Name

Paracetamol 500 mg, diphenhydramine hydrochloride 25 mg.



CAS numbers: Paracetamol: 103-90-2 Diphenhydramine hydrochloride: 147-24-0

DESCRIPTION

Paracetamol and diphenhydramine film coated tablets.

Excipients: Maize starch, potassium sorbate, povidone, croscarmellose sodium, purified talc, stearic acid, Opadry complete film coating system 03F505035 Blue.

PHARMACOLOGY

Pharmacokinetics. Paracetamol. Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration. Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. The elimination half-life varies from about 1 to 3 hours.

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged.

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 overdose (more than 150 mg/kg or 10 g total paracetamol ingested) and if left untreated can cause irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, infants and young children compared to adults, the sulfate conjugate being predominant.

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. The sedative effect also appears to be maximal within 1-3 hours after administration of a single dose. It is positively correlated with the plasma drug concentration. Diphenhydramine is widely distributed throughout the body, including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly (approx. 80-85%) bound to plasma proteins. Metabolism is extensive, mainly in the liver. Multiple cytochrome P450 enzymes contribute to the metabolism of diphenhydramine, including CYP2D6. The drug is metabolised principally to diphenylmethoxyacetic acid and is also dealkylated. It undergoes first-pass metabolism in the liver and only about 40-60% of an oral dose reaches systemic circulation as unchanged diphenhydramine. The metabolites are conjugated with glycine and glutamine and excreted in urine. Diphenhydramine is excreted mainly in the urine as metabolites; little (about 1%) is excreted as unchanged substance. The elimination half-life has been reported to range from 2.4 to 9.3 hours in healthy adults. The terminal elimination half-life is prolonged in liver cirrhosis.

Pharmacodynamics/ mechanism of action. Paracetamol. Paracetamol is a p-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity. Paracetamol is thought to produce analgesia through a central inhibition of prostaglandin synthesis.

The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is, therefore, particularly suitable for patients with a history of disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride competes with histamine at central and peripheral histamine -receptor sites, preventing the histamine₁-receptor interaction and subsequent mediator release.

Diphenhydramine is a highly lipophilic molecule that readily crosses the blood brain barrier.

Diphenhydramine is highly selective for histamine₁-receptors but has little effect on histamine₂ or histamine₃-receptors. Diphenhydramine also activates 5-hydroxytryptamine (serotonin) and α -adrenergic receptors and blocks cholinergic receptors.

Diphenhydramine is effective in reducing sleep onset (i.e. time to fall asleep) and increasing the depth and quality of sleep.

CLINICAL TRIALS

Not Applicable

INDICATIONS

For the temporary relief of pain when associated with sleeping difficulty, for example: headache, migraine, backache, arthritis, rheumatic and muscle pain, neuralgia, toothache or period pain. Relief of fever.

CONTRAINDICATIONS

Not for use in children 12 years of age and younger.

Not for use for anyone with hypersensitivity to paracetamol, diphenhydramine hydrochloride or to any of the excipients.

Caution should be exercised in patients with the following:

- Narrow angle glaucoma
- Stenosing peptic ulcer
- Symptomatic prostatic hypertrophy
- Bladder neck obstruction
- Pyloroduodenal obstruction

Diphenhydramine is contraindicated for use in the following:

- Newborns or premature infants
- Lactating women
- Patients taking monoamine oxidase inhibitors (MAOIs)

See INTERACTIONS WITH OTHER MEDICINES for additional information.

PRECAUTIONS

MersynoNight Night Time Pain Relief should be used with care in patients with:

- impaired hepatic function;
- impaired renal function.

Underlying liver disease increases the risk of paracetamol related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Contains paracetamol. Do not use with any other paracetamol containing products. The concomitant use with other products containing paracetamol may lead to overdose.

Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic have a low body mass index or are chronic heavy users of alcohol.

In patients with depleted glutathione states such as sepsis the use of paracetamol may increase the risk of metabolic acidosis.

Caution should be exercised in patients with epilepsy or seizure disorders, myasthenia gravis, prostatic hypertrophy, urinary retention, asthma, bronchitis and chronic obstructive pulmonary disease (COPD).

Diphenhydramine hydrochloride may cause drowsiness and may increase the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

Do not take for more than 3 days without consulting a doctor. If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

Use with caution with:

- drugs with antimuscarinic properties, e.g. atropine, tricyclic antidepressants.

See Interactions with Other Medicines for additional information.

Use in pregnancy

Category A: Both paracetamol and diphenhydramine have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

This product is not to be used during pregnancy without medical advice.

Use of sedating antihistamines during the third trimester may result in reactions in the newborn or premature neonates.

Use in lactation.

MersynoNight Night Time Pain Relief tablets should not be used whilst breastfeeding.

Paracetamol is excreted in small amounts (<0.2%) in breast milk. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infant.

Diphenhydramine is excreted in breast milk. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

Paediatric use

Children may experience paradoxical excitation with diphenhydramine.

MersynoNight Night Time Pain Relief tablets are not recommended for use in children under 12 years of age.

Use in the elderly

The elderly may experience paradoxical excitation with diphenhydramine. The elderly are more likely to have central nervous system (CNS) depressive side effects including confusion (see CONTRAINDICATIONS)

Effects on ability to drive and use machines

MersynoNight Night Time Pain Relief tablets may cause drowsiness, dizziness, blurred vision, cognitive and psychomotor impairment which can seriously affect the patient's ability to drive or operate machinery. If affected, do not drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES

The following interactions with paracetamol have been noted.

Anticoagulant drugs (warfarin): dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.

Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.

Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.

Paracetamol may increase chloramphenicol concentrations.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.

Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.

Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

The following interactions with diphenhydramine hydrochloride have been noted.

Central nervous system (CNS) depressants (alcohol, sedatives, opioid analgesics, hypnotics): may cause an increase in sedation effects.

Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs): may prolong and intensify the anticholinergic and CNS depressive effects.

Diphenhydramine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with drugs that are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.

Avoid use with other antihistamine containing preparations including topical preparations and cough and cold medicines.

ADVERSE EFFECTS

Paracetamol. Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol, if left untreated, can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive postmarketing experience at therapeutic/ labelled dose and considered attributable are listed below by system organ class and frequency.

As the adverse reactions identified from postmarketing use are reported voluntarily from a population of uncertain size, the frequency is not known but likely to be very rare.

Blood and lymphatic system disorders. Thrombocytopenia.

Immune system disorders. Anaphylaxis, cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens-Johnson syndrome.

Respiratory, thoracic and mediastinal disorders. Bronchospasm in patients sensitive to aspirin and other NSAIDs.

Hepatobiliary disorders. Hepatic dysfunction.

Diphenhydramine. *Central nervous system (CNS) effects.* CNS depressive effects of diphenhydramine hydrochloride include sedation and impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills and impaired information processing). Performance may be impaired in the absence of sedation and may persist the morning after a night time dose.

CNS stimulatory effects of diphenhydramine may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of diphenhydramine may cause nervousness, tremor, insomnia, agitation and irritability.

Anticholinergic effects. Side effects of diphenhydramine associated with cholinergic blockage include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.

Adverse reactions that have been observed in clinical trials and which are considered to be common or very common are listed below. The frequency of other adverse reactions identified during postmarketing use is not known but these reactions are likely to be uncommon or rare.

General disorders and administration site conditions. Common (1/10-1/100): fatigue.

Immune system disorders. Not known: hypersensitivity reaction including rash, urticaria, dyspnoea and angioedema.

Psychiatric disorders. Not known: confusion, paradoxical excitation (e.g. increased energy, restlessness, nervousness).

The elderly are more prone to confusion and paradoxical excitation.

Nervous system disorders. Common (1/10-1/100): sedation, drowsiness, disturbance in attention, unsteadiness, dizziness. Not known: convulsions, headache, paraesthesia, dyskinesias.

Eye disorders. Not known: blurred vision.

Cardiac disorders. Not known: tachycardia, palpitations.

Respiratory, thoracic and mediastinal disorders. Not known: thickening of bronchial secretions.

Gastrointestinal disorders. Common (1/10-1/100): dry mouth. Not known: gastrointestinal disturbance including nausea, vomiting.

Musculoskeletal and connective tissue disorders. Not known: muscle twitching.

Renal and urinary disorders. Not known: urinary difficulty, urinary retention.

DOSAGE AND ADMINISTRATION

Adults and children over 12 years. Take 2 tablets with water or other fluid only at bedtime. Maximum of two tablets in 24 hours. Do not exceed the stated dose.

Do not use in children under 12 years of age.

Other products containing paracetamol may be taken during the day but the total daily dose of paracetamol must not exceed 4,000 mg in any 24 hour period. Allow at least four hours between taking any paracetamol containing product and MersynoNight Night Time Pain Relief tablets.

For adults, paracetamol should not be taken for more than a few days at a time except on medical advice.

For children, paracetamol should not be taken for more than 48 hours except on medical advice.

OVERDOSAGE

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126) for advice, or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

Diphenhydramine overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes. Large overdose may cause

rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse.

Treatment. Paracetamol. Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. Administration of N-acetylcysteine or methionine may be required.

Diphenhydramine. Treatment should be supportive and directed towards specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

PRESENTATION AND STORAGE CONDITIONS

Blue colour, capsule shaped film coated tablet debossed with “PD5” on one side and plain on the other side. PVC/Al blister packs of 4, 10, 12 or 20 tablets.

Store below 25°C. Protect from moisture.

Note: Not all pack sizes may be available.

NAME AND ADDRESS OF THE SPONSOR

Sanofi Consumer Healthcare
87 Yarraman Place, Virginia, QLD 4014,
Australia

POISONS SCHEDULE OF THE MEDICINE

S3 – Pharmacist Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

28 March 2018

DATE OF MOST RECENT AMENDMENT