

New Zealand Data Sheet

Product description

Pharmacist's Own™ Pain Relief Plus

Paracetamol 450 mg per tablet, Codeine phosphate 9.75 mg per tablet and Doxylamine succinate 5 mg per tablet.

Blister pack of 24 flat, yellow tablets with a centre break-line.

Contains the following ingredients as excipients:

- Microcrystalline cellulose
- Crospovidone
- Magnesium stearate
- Povidone
- Quinoline yellow
- Sunset yellow FCF
- Pregelatinised Starch
- Stearic Acid

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 150mg/kg or 10g 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.

Codeine phosphate

Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma-codeine concentrations occur at about one hour after ingestion of codeine phosphate.

Codeine is metabolised by O- and N-demethylation in the liver (via the cytochrome P450 system) to morphine (about ten per cent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Approximately 3% to 16% of a dose is eliminated unchanged in the urine.

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.

Doxylamine succinate

Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration, the mean peak plasma concentration occurs after 2-3 hours. It has an elimination half-life of about 10 hours in healthy adults. It is excreted in the urine as unchanged doxylamine (60%) and metabolites (nordoxylamine and dinordoxylamine).

The major metabolic site is the liver and major metabolic pathways are N-demethylation, N-oxidation, hydroxylation, N-acetylation, N-desalkylation and ether cleavage.

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.

Codeine Phosphate

Codeine acts centrally. It has an analgesic effect, which is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine.

Doxylamine Succinate

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

Doxylamine succinate is a highly lipophilic molecule that readily crosses the blood-brain barrier.

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

Doxylamine has pronounced sedative effects.

The combination of codeine, paracetamol and doxylamine produces greater analgesia than any of these drugs alone and avoids the side effects associated with large doses of the components.

Indications

Pharmacist's Own™ Pain Relief Plus provides effective pain relief from

- tension and migraine headache,
- muscular pain,
- period pain, and
- back pain.

Contraindications

Paracetamol

Paracetamol is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol (or any of the other ingredients in the product).

Refer to 'Interactions with other medicines' for additional information.

Codeine phosphate

Codeine is contraindicated for use in patients:

- with known hypersensitivity or idiosyncratic reaction to codeine (or any of the other ingredients in the product);
- with acute respiratory depression;
- with obstructive airways disease
- with acute alcoholism;
- with head injuries or conditions in which intracranial pressure is raised;
- at risk of paralytic ileus;
- with hepatic failure;
- with acute asthma attack;
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate;
- with chronic constipation;
- 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).

Refer to 'Interactions with other medicines' for additional information.

Doxylamine succinate

Doxylamine succinate is contraindicated for use:

- in patients with a history of hypersensitivity to the substance or substances of similar chemical structure (or any of the other ingredients in the product);
- in patients with narrow-angle glaucoma;
- in patients with stenosing peptic ulcer;
- in patients with symptomatic prostatic hypertrophy;
- in patients with bladder neck obstruction;
- in patients with pyloroduodenal obstruction.
- newborns or premature infants;
- lactating women;
- patients taking monoamine oxidase inhibitors (MAOIs).

Refer to 'Interactions with other medicines' for additional information.

Warnings & Precautions

Paracetamol

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

- impaired hepatic function;
- impaired renal function.

Codeine phosphate

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

- hypothyroidism;
- adrenocortical insufficiency e.g. Addison's Disease;
- hepatic or renal impairment;
- prostatic hypertrophy;
- shock/ hypotension;
- myasthenia gravis;
- convulsions/ convulsive disorders;
- gall bladder disease or gall stones;
- recent gastrointestinal tract 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 such treatment;
- a history of drug abuse;
- are taking other respiratory depressants or sedatives, including alcohol.

Codeine may obscure the diagnosis or the course of gastrointestinal diseases.

Doxylamine succinate

Doxylamine succinate should be used with caution in patients with the following conditions:

- renal or hepatic impairment;
- epilepsy.

Hypersensitivity

Codeine phosphate

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

Dependence

Codeine phosphate

Taking codeine regularly for a long time can lead to addiction. Stopping treatment can result in withdrawal symptoms. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for headache can result in an overuse syndrome.

Withdrawal

Codeine phosphate

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.

Genetic polymorphism

Codeine phosphate

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

Paracetamol, Codeine Phosphate and Doxylamine Succinate have all 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.

The balance of benefits and risks should be carefully considered.

Codeine phosphate

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.

Use in Lactation

Although Paracetamol is only excreted in small amounts in breast milk, both codeine and doxylamine are excreted in breast milk and therefore this product is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

Codeine phosphate

Codeine is excreted into breast milk. However at usual analgesic doses, concentrations are usually low. However, infants of nursing 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. Nursing patients should be told how to recognise signs of high morphine levels in themselves and their babies.

Signs of high morphine levels in a mother are 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. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice.

Use in children

Not recommended for children under 12 years of age.

Codeine phosphate

Children up to two years of age may be more susceptible to the effects, especially the respiratory depressant effects of opioid analgesics. Paradoxical excitation is especially likely to occur in paediatric patients receiving these medicines.

Doxylamine succinate

Children may experience paradoxical excitation with doxylamine succinate. (See contraindications).

Use in the elderly

Codeine phosphate

Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects of medications containing codeine. 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.

Doxylamine succinate

The elderly may experience paradoxical excitation with doxylamine succinate. They are more likely to have central nervous system (CNS) depressive side effects, including confusion. (See contraindications).

Effect on ability to drive and operate machinery

Codeine phosphate

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.

Doxylamine succinate

Doxylamine succinate may

- cause drowsiness which may continue the following day.
- increase the effects of alcohol.

Those affected should not drive or operate machinery; alcohol should be avoided.

Interaction with other medicines

Paracetamol

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.

Codeine phosphate

The following interactions with codeine have been noted:

- Monoamine oxidase inhibitors (MAOIs) – due to the possible risk of excitation or depression, avoid concomitant use and for 14 days after discontinuation of MAOI.
- 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 and domperidone – antagonistic effects on gastrointestinal activity.
- Anti-diarrhoeal drugs – increased risk of severe constipation.
- Anaesthetics – enhanced sedative effect.
- Tricyclic antidepressants – enhanced sedative effect.
- Antipsychotics – enhanced sedative and hypotensive effect.
- Opioid antagonists – may precipitate withdrawal symptoms
- Quinidine – reduced analgesic effect
- Antihypertensives – hypotensive effects may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.
- Ciprofloxacin – avoid premedication with opioids as they reduce ciprofloxacin concentration.
- Ritonavir – may increase plasma levels of opioid analgesics
- Mexiletine – delayed absorption of mexiletine
- Cimetidine – inhibits the metabolism of opioid analgesics causing increased plasma codeine concentrations.
- CNS depressants – concomitant use with central nervous system depressants (e.g. barbiturates, chloral hydrate, sedatives, alcohol and centrally acting muscle relaxants) can cause additive CNS depression.

Doxylamine succinate

The following interactions with doxylamine succinate 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.

Adverse reactions

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.

Codeine phosphate

The most common adverse effects associated with codeine are nausea, vomiting, drowsiness, dizziness and constipation.

Other side effects are rare, especially at OTC dosage levels.

Known adverse reactions include:

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

Nervous system disorders – confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucination, CNS excitation (restlessness/excitation), 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 diminished 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.

Doxylamine succinate

Central Nervous System (CNS) effects –

- CNS depressive effects of doxylamine succinate 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 doxylamine succinate may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

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

Anticholinergic effects –

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

Dosage (Keep to the Recommended Dosage)

Adults and children 12 years and over: Take 1 - 2 tablets with water, every 4 to 6 hours as required.

Do not exceed 8 tablets in 24 hours.

Do not halve tablets. Dose equivalence when the tablet is divided has not been established.

Use in adults

Should not be taken for more than three days at a time except on medical advice.

Use in children

Not recommended for children under 12 years of age. Children and Adolescents should not take this product for more than 48 hours except on medical advice.

Overdosage

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in New Zealand call 0800 764 766) for advice, or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Presentation

Pharmacist's Own™ Pain Relief Plus is a blister pack of 24 flat, yellow tablets with a centre break line. Do not halve tablets. Dose equivalence when the tablet is divided has not been established.

Medicines Classification

Pharmacist Only Medicine

Name and Address of Sponsor

PSM Healthcare Ltd trading as API Consumer Brands
PO Box 76 401
Manukau City
Auckland 2241
New Zealand

Prepared

9th March 2011