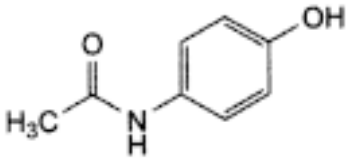
APOHEALTH COLD & FLU RELIEF DAY/NIGHT

NAME OF THE MEDICINE

Paracetamol

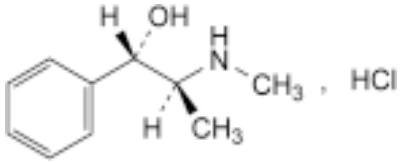


Molecular Formula:
$C_8H_9NO_2$

Molecular Weight: 151.2

CAS No.: 103-90-2

Pseudoephedrine hydrochloride

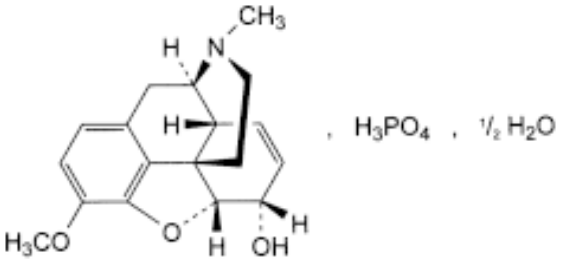


Molecular Formula:
$C_{10}H_{16}ClNO$

Molecular Weight: 201.7

CAS No.: 345-78-8

Codeine phosphate

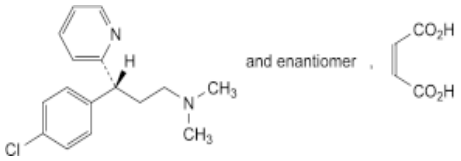


Molecular Formula:
$C_{18}H_{24}NO_7P,½H_2O$

Molecular Weight: 406.4

CAS No.: 41444-62-6

Chlorpheniramine maleate



Molecular Formula:
$C_{20}H_{23}ClN_2O_4$

Molecular Weight: 390.9

CAS No.: 113-92-8

DESCRIPTION

Each Apohealth Cold & Flu Relief Day/Night Tablets Day tablet contains the active ingredients:

- Paracetamol 500mg
- Pseudoephedrine hydrochloride 30mg
- Codeine phosphate 6mg

It also contains:

- Cellulose - microcrystalline
- Crospovidone
- Magnesium stearate
- Povidone
- Starch-pre-gelatinised
- Stearic acid

Each Apohealth Cold & Flu Relief Day/Night Tablets Night tablet contains the active ingredients:

- Paracetamol 500mg
- Pseudoephedrine hydrochloride 30mg
- Chlorpheniramine maleate 2mg

It also contains:

- Cellulose - microcrystalline
- Crospovidone
- Erythrosine
- Magnesium stearate
- Povidone
- Starch – pregelatinised maize
- Stearic acid

Paracetamol is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Pseudoephedrine hydrochloride is a white or almost white crystalline powder or colourless crystals. It is freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride. Its melting point is at about 184^0C.

Codeine phosphate is a white or almost white crystalline powder or small, colourless crystals. It is freely soluble in water, and slightly soluble or very slightly soluble in ethanol (96 per cent).

Chlorpheniramine maleate is a white or almost white, crystalline powder. It is freely soluble in water and soluble in ethanol (96 per cent).

PHARMACOLOGY

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.

Pseudoephedrine has direct- and indirect- sympathomimetic activity and is an effective decongestant in the upper respiratory tract. It is a stereoisomer of ephedrine and has a similar action, but has been found to have less pressor activity and fewer central nervous system (CNS) effects. Sympathomimetic agents are used as nasal decongestants to provide symptomatic relief. They act by causing vasoconstriction resulting in redistribution of local blood flow to reduce oedema of the nasal mucosa, thus improving ventilation, drainage and nasal stuffiness.

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.

Chlorpheniramine competes with histamine at central and peripheral histamine$_1$-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release. It is a highly lipophilic molecule that readily crosses the blood-brain barrier. It is highly selective for histamine$_1$-receptors but has little effect on histamine$_2$ or histamine$_3$ receptors. Chlorpheniramine also activates 5-hydroxytryptamine (serotonin) and α-adrenergic receptors and blocks cholinergic receptors.

Pharmacokinetics

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration.

Pseudoephedrine is readily absorbed from the gastrointestinal tract.

Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma-codeine concentrations occurring about one hour after ingestion of codeine phosphate.
Chlorpheniramine maleate is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Bioavailability is low, values of 25 to 50% having been reported. A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters. More rapid and extensive absorption has been reported in children compared to adults.

Distribution

Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. Paracetamol crosses the placenta and is present in breast milk.

Small amounts of pseudoephedrine are distributed into breast milk.

Codeine is distributed into skeletal muscles, kidneys, liver, gastrointestinal tract, lungs, spleen and brain. Codeine crosses the placenta and is distributed into breast milk.

Chlorpheniramine is widely distributed in the body and enters the CNS. About 70% of chlorpheniramine in the circulation is bound to plasma proteins.

Metabolism

Paracetamol is metabolised extensively in the liver. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage (more than 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.

Pseudoephedrine is incompletely metabolised (less than 1%) in the liver to an inactive metabolite by N-demethylation.

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. About 8% of people metabolise drugs poorly via CYP2D6, and are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine.

Chlorpheniramine maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorpheniramine. Chlorpheniramine appears to undergo considerable first-pass metabolism.

Excretion

Paracetamol is excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged. The elimination half-life varies from about 1 to 3 hours.

Pseudoephedrine is largely excreted unchanged in the urine, together with small amounts of its hepatic metabolite. It has a half-life of about 5-8 hours; elimination is enhanced and half-life reduced accordingly in acid urine.

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. The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

Unchanged chlorpheniramine and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces. There is wide inter-individual variation in the pharmacokinetics of chlorpheniramine; half-life values ranging from 2 to 43 hours have been reported. Faster clearance and a shorter half-life have been reported in children compared to adults.

INDICATIONS

Apohealth Cold & Flu Relief Day/Night Tablets are indicated for the temporary relief of the symptoms of cold and flu symptoms. The day tablets relieve headache, body aches and pains, fever, nasal congestion and runny nose. The night tablets relieve headache, body aches and pains, fever, watery eyes, sneezing, nasal congestion and runny nose.

CONTRAINDICATIONS

Apohealth Cold & Flu Relief Day/Night Tablets are contraindicated for use in patients with the following conditions:

- Known hypersensitivity or idiosyncratic reaction to paracetamol, pseudoephedrine, codeine, other opiates, chlorpheniramine (or substances of a similar chemical structure), or any of the other ingredients in this medicine.
- Severe hypertension or coronary artery disease.
- Taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days.
- Acute respiratory depression.
- Chronic constipation.
- During labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate.
- Active alcoholism.
- 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).
- Narrow-angle glaucoma.
- Stenosing peptic ulcer.
- Symptomatic prostatic hypertrophy.
- Bladder neck obstruction.
- Pyloroduodenal obstruction.
- Lactating women.

Refer also to ‘Interactions with other medicines’ for additional information.

PRECAUTIONS

Apohealth Cold & Flu Relief Day/Night Tablets should be used with caution in patients with the following conditions:

- Impaired hepatic function.
- Impaired renal function.
- Hypertension.
- Hypotension.
- Hyperthyroidism.
- Hypothyroidism.
- Diabetes mellitus.
- Coronary heart disease.
- Ischaemic heart disease.
- Glaucoma.
- Prostatic hypertrophy.
- Decreased respiratory reserve e.g. asthma or COPD.
- Pre-existing respiratory depression.
- History of drug abuse.

- Raised intracranial pressure or head injury.
- Taking other respiratory depressants or sedatives, including alcohol.
- Have had recent gastrointestinal tract surgery.
- Epilepsy.

Codeine may obscure the diagnosis or the course of gastrointestinal diseases.
Prolonged use of codeine may produce physical and psychological dependence.
Codeine may cause drowsiness. Those affected should not drive or operate machinery.

Chlorpheniramine 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.

This medicine contains pseudoephedrine which may cause sleeplessness if taken up to several hours before going to bed.

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

Use in pregnancy

Category B2: Pseudoephedrine has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data shows no evidence of an increased occurrence of foetal damage.

Opioid analgesics may cause respiratory depression in the newborn infant. Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate (see Contraindications).

Apohealth Cold & Flu Relief Day/Night Tablets should not be used in pregnancy unless the potential benefits to the patient are weighed against the possible risk to the foetus.

Use in lactation

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 infants.

It has been estimated that 0.5% to 0.7% of a single dose of pseudoephedrine ingested by the mother will be excreted in the breast milk over 24 hours.

Trace amounts of codeine are excreted into breast milk.

Chlorpheniramine is excreted in breast milk.

Therefore, Apohealth Cold & Flu Relief Day/Night Tablets are not recommended for breastfeeding mothers (see also Contraindications).

Use in the elderly

The elderly are more likely to have age related renal impairment and may be more susceptible to the respiratory depressant effects of codeine.

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

Use in children

Children may experience paradoxical excitation with chlorpheniramine.

Carcinogenicity

Toxicity studies in animals have shown that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis; the relevance of this finding to use in humans is not known.

Effects on Laboratory Tests

Plasma amylase and lipase activity: Codeine may cause increased biliary tract pressure, thus increasing plasma amylase and/or lipase concentrations.

Gastric emptying studies: Gastric emptying is delayed by codeine so gastric emptying studies will not be valid.

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 pseudoephedrine have been noted:

- Antidepressant medication e.g. tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) – may cause a serious increase in blood pressure or hypertensive crisis.
- Other sympathomimetic agents, such as decongestants, appetite suppressants and amphetamine-like psychostimulants – may cause an increase in blood pressure and additive effects.
- Methyldopa and β-blockers – may cause an increase in blood pressure.
- Urinary acidifiers enhance elimination of pseudoephedrine.
- Urinary alkalinisers decrease elimination of pseudoephedrine.

The following interactions with codeine have been noted:

- 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.
- Anticholinergics – concurrent use of codeine with anticholinergic agents may increase the risk of severe constipation and/or urinary retention.
- Antihypertensives – hypotensive effects may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.
- Antiperistaltic antidiarrhoeals (e.g. kaolin, pectin and loperamide) – concurrent use with codeine may increase the risk of severe constipation.
- Metoclopramide – codeine may antagonise the effects of metoclopramide on gastrointestinal activity.

- Monoamine oxidase inhibitors (MAOIs) – concurrent administration or use within 14 days of ceasing MAOIs may enhance the potential respiratory depressant effects of codeine.
- Opioid analgesics – concurrent use of codeine and other opioid receptor antagonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur.
- Substances that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.
- Tranquillisers, sedatives and hypnotics – codeine may potentiate the effects of these preparations.

The following interactions with chlorpheniramine 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.
- When taken concomitantly with phenytoin may cause a decrease in phenytoin elimination.

ADVERSE EFFECTS

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 effects of pseudoephedrine include:
- Cardiovascular stimulation – elevated blood pressure, tachycardia or arrhythmias.
- Central nervous system (CNS) stimulation – restlessness, insomnia, anxiety, tremors and (rarely) hallucinations.
- Skin rashes.
- Urinary retention.

Children and the elderly are more likely to experience adverse effects than other age groups.

The most common side effects associated with codeine are:
- Nausea, vomiting, constipation.
- Drowsiness, dizziness.

Other side effects are rare, especially at OTC levels. These include:
- Cough suppression.
- Respiratory depression.
- Euphoria, dysphoria.
- Skin rashes.
- Histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

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

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

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

DOSAGE & ADMINISTRATION

Adults and children over 12 years:
Take 2 white day tablets in the morning and in the afternoon when necessary, with water.
Take 2 pink Night tablets at bedtime if required.

Dose may be repeated after 4 – 6 hours if required.

Do not exceed 4 doses (a total of 8 tablets) in 24 hours.

Do not take the Night tablet within 4 hours or taking the Day tablet.

Do not take more than the recommended dose.

This medicine should not be taken with other medicines containing paracetamol unless advised to do so by a doctor or pharmacist.

Use in adults
This medicine should not be taken for more than a few days at a time except on medical advice.

Use in children
This medicine should not be taken for more than 48 hours except on medical advice.

Do not give to children under 12 years.

OVERDOSAGE

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126; 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 AND STORAGE CONDITIONS

Apohealth Cold & Flu Relief Day/Night Tablets are:
Day Tablet: a flat white tablet with bevelled edges.
Night Tablet: a pink, round tablet with a breakline.

The tablets are presented in PVC/PVDC/Aluminium blister packs which are enclosed in a carton. Each blister pack contains 8 Day Medication white tablets and 4 Night Medication pink tablets.

The pack sizes are
- 24 tablets (2 x 12 tablet blister packs in a carton).

Apohealth Cold & Flu Relief Day/Night Tablets should be stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Apohealth Cold & Flu Relief Day/Night Tablets is supplied by:

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Pharmacist Only Medicine (S3)

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

16 April 2014

AUST R 236266

DATE OF MOST RECENT AMMENDMENT

27th March 2015