PRODUCT INFORMATION

Codral* Original Day & Night Cold & Flu Tablets

Product description

Codral* Original Day & Night Cold & Flu tablets contain two separate formulations: day tablets and night tablets.

Each Codral* Original Day & Night Cold & Flu **day** tablet contains paracetamol 500 mg, pseudoephedrine hydrochloride 30 mg, codeine phosphate 6 mg

and the excipients: microcrystalline cellulose, hydroxypropylcellulose, lactose, magnesium stearate, sodium starch glycollate, pregelatinised wheat starch, stearic acid.

Each Codral* Original Day & Night Cold & Flu **night** tablet contains paracetamol 500 mg, pseudoephedrine hydrochloride 30 mg, triprolidine hydrochloride 1.25 mg

and the excipients: brilliant blue FCF, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, povidone, quinoline yellow.

Pharmacology

Pharmacokinetics

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 overdosage (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.

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It 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. Small amounts are distributed into breast milk.

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.

After absorption from the gastro-intestinal tract, triprolidine hydrochloride is metabolised; a carboxylated derivative accounts for about half the dose excreted in the urine. Reported half-lives vary from 3 to 5 hours or more. Triprolidine is distributed into breast milk.

Pharmacodynamics/Mechanism of action

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.

Triprolidine competes with histamine at central and peripheral histamine$_1$-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release.

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

Triprolidine is highly selective for histamine$_1$-receptors but has little effect on histamine$_2$ or histamine$_3$ receptors. Triprolidine also activate 5-hydroxytryptamine (serotonin) and α-adrenergic receptors and blocks cholinergic receptors.

Indications

Codral* Original Day & Night Cold & Flu provides fast and effective temporary relief from the symptoms of cold and flu. The day tablets relieve the symptoms of cold and flu during the day. The night tablets relieve the symptoms of cold and flu aiding restful sleep.

Contraindications

Paracetamol is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol (or any of the other ingredients in the product). Use of the product should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudoephedrine is contraindicated for use in patients:

- with known hypersensitivity or idiosyncratic reaction to pseudoephedrine (or any of the other ingredients in the product)
- with severe hypertension or coronary artery disease
- taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days.

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 chronic constipation
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate
- with 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).
- who are CYP2D6 ultra-rapid metabolisers. Even at labelled dosage regimens, ultra-rapid metabolisers of codeine may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

Use of the drug should be discontinued and quick medical attention should be sought at the earliest sign of codeine toxicity including symptoms such as extreme sleepiness, confusion, or shallow breathing, which may be life threatening.

Triprolidine 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)
- narrow-angle glaucoma
- stenosing peptic ulcer
- symptomatic prostatic hypertrophy

- bladder neck obstruction
- pyloroduodenal obstruction.

Triprolidine is contraindicated for use in:
- newborns or premature infants
- lactating women
- patients taking monoamine oxidase inhibitors (MAOIs).

Refer to ‘Interactions with other drugs’ for additional information.

Precautions

Paracetamol should be used with caution in patients with:
- impaired hepatic function
- impaired renal function
- chronic alcoholism

Pseudoephedrine should be used with caution in patients with:
- hypertension
- hyperthyroidism or thyroid disease
- diabetes mellitus
- coronary heart disease
- ischaemic heart disease
- glaucoma
- prostatic hypertrophy
- severe hepatic or renal dysfunction.

Codeine should be used with caution in patients:
- with decreased respiratory reserve e.g. emphysema, chronic bronchitis, asthma or COPD
- with pulmonary oedema
- with pre-existing respiratory depression
- aged 12-18 years who have breathing problems
- who have a history of drug abuse
- who are taking other respiratory depressants or sedatives, including alcohol
- who have had recent gastrointestinal tract surgery
- with obstructive bowel disorders
- at risk of paralytic ileus
- who are at risk for additive CNS effects
- with convulsive disorders
- with raised intracranial pressure or head injury
- with prostatic hypertrophy
- with hepatic or renal impairment
- with hypotension
- with hypothyroidism
- who are breastfeeding

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

Prolonged use of codeine may produce tolerance, physical and psychological dependence.

Codeine may cause drowsiness. Those affected should not drive or operate machinery.

Triprolidine 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.

Use with caution in patients with renal or hepatic impairment, patients with epilepsy, and patients with respiratory conditions such a emphysema, chronic bronchitis or acute or chronic bronchial asthma.

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

Use in children and 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.

Children and the elderly may experience paradoxical excitation with the active ingredient, triprolidine. The elderly are more likely to have CNS depressive side effects, including confusion.

Use in pregnancy: Category B2

Paracetamol has 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.

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.

Pseudoephedrine should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus.
Codeine has 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.

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.

Triprolidine has 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.

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 infant.

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

At labelled doses, trace amounts of codeine are excreted into breast milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, some women are ultra-rapid metabolisers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Deaths have occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolisers of codeine. Maternal use of codeine can lead to serious adverse reactions, including death, in nursing infants. Codeine is contraindicated in breast-feeding women.

Triprolidine 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.

Interactions with other drugs
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 eg 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 CNS 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 triprolidine have been noted:

- 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

Adverse drug reactions identified during post-marketing experience are detailed in the tables below. Additionally, the following should be noted:

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported.

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 elevated blood pressure.

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

One of the common adverse effects associated with codeine is drowsiness.

Other side effects are rare, especially at OTC dosage levels. These include: cough suppression, dysphoria, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

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

High doses of triprolidine may cause agitation, and irritability.

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

DAY CAPSULE: Adverse drug reactions identified during post-marketing experience with paracetamol, pseudoephedrine or the combination and with codeine appear in the following table. The frequency category was estimated from spontaneous reporting rates.

Frequency category	Adverse Event Preferred Term
Immune System Disorders	
Very Rare	*Anaphylactic reaction*
Very Rare	*Hypersensitivity*
Psychiatric Disorders	
Very Rare	*Anxiety*
Very Rare	*Euphoric mood*
Nervous System Disorders	
Very Rare	*Vertigo*
Very Rare	*Headache*
Very Rare	*Psychomotor hyperactivity (in the pediatric population)*

Very Rare	*Sedation*
Cardiac Disorders	
Very Rare	*Arrhythmia*
Very Rare	*Palpitations*
Very Rare	*Tachycardia*
Respiratory,Thoracic, and Mediastinal Disorders	
Very Rare	*Bronchospasm*
Very Rare	*Respiratory depression*
Gastrointestinal Disorders	
Very Rare	*Abdominal Pain*
Very Rare	*Dyspepsia*
Very Rare	*Constipation*
Very Rare	*Diarrhoea*
Very Rare	*Nausea*
Very Rare	*Vomiting*
Skin and Subcutaneous Tissue Disorders	
Very Rare	*Pruritus*
Very Rare	*Angioedema*
Very Rare	*Pruritic rash*
Very Rare	*Dermatitis*
Very Rare	*Rash*
Very Rare	*Urticaria*
Renal and Urinary Disorders	
Very Rare	*Dysuria*
Very Rare	*Urinary retention*
General Disorders and Administration Site Conditions	
Very Rare	*Feeling jittery*
Investigations	
Very Rare	*Transaminases increased*

Dependence of the morphine type can develop following long-term use of high doses.

NIGHT CAPSULE: Adverse drug reactions identified during post-marketing experience with paracetamol, pseudoephedrine, the combination of pseudoephedrine and triprolidine, the combination of pseudoephedrine and paracetamol or the combination paracetamol, pseudoephedrine and triprolidine appear in the following table. The frequency category was estimated from spontaneous reporting rates.

Frequency category	Adverse Event Preferred Term
Immune System Disorders	
Very Rare	*Anaphylactic reaction*
Very Rare	*Hypersensitivity*
Psychiatric Disorders	
Very Rare	*Hallucination*
Very Rare	*Anxiety*
Very Rare	*Euphoric mood*
Very Rare	*Insomnia*
Very Rare	*Nervousness*
Very Rare	*Restlessness*
Nervous System Disorders	
Very Rare	*Dizziness*
Very Rare	*Headache*
Very Rare	*Paraesthesia*
Very Rare	*Psychomotor hyperactivity (in the pediatric population)*
Very Rare	*Somnolence*
Very Rare	*Tremor*
Cardiac Disorders	
Very Rare	*Arrhythmia*
Very Rare	*Palpitations*
Very Rare	*Tachycardia*
Respiratory,Thoracic, and Mediastinal Disorders	
Very Rare	*Epistaxis*
Gastrointestinal Disorders	
Very Rare	*Abdominal Discomfort*
Very Rare	*Dry mouth*
Very Rare	*Nausea*
Very Rare	*Vomiting*
Skin and Subcutaneous Tissue Disorders	
Very Rare	*Pruritus*

Very Rare	*Angioedema*
Very Rare	*Pruritic rash*
Very Rare	*Rash*
Very Rare	*Urticaria*
Renal and Urinary Disorders	
Very Rare	*Dysuria*
Very Rare	*Urinary retention*
General Disorders and Administration Site Conditions	
Very Rare	*Fatigue*
Very Rare	*Feeling jittery*
Investigations	
Very Rare	*Blood pressure increased*
Very Rare	*Transaminases increased*

Dosage

The recommended dosages of Codral* Original Day & Night Cold & Flu for adults and children 12 years and over are as follows:

- Day – 2 white day tablets in the morning and again in the afternoon.
- Night – 2 blue night tablets at bedtime.

Codral* Original Day & Night Cold & Flu should not to be used for children under twelve years of age.

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

Use in 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 13 11 26; 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

Codral* Original Day & Night Cold & Flu day tablets are round, white, bevelled, biconvex and uncoated. They are scored and branded ‘K7F’ on one face, and plain on the other face.

Codral* Original Day & Night Cold & Flu night tablets are turquoise, bevelled, capsule-shaped, flat and uncoated. They are scored on one face and coded ‘S3F’ each side of the score, and plain on the other face.

Codral* Original Day & Night Cold & Flu tablets are available in blister packs of the following sizes:

- 6 tablets (S3) Pharmacist Only Medicine
- 24 tablets[#] (S3) Pharmacist Only Medicine
- 48 tablets (S4) Prescription Only Medicine

[#] marketed

Store below 25°C. Store in a dry place, away from direct light.

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Name and Address of Sponsor

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*Registered trademark

TGA approved: 28 September 2006
Date of most recent amendment: 25 November 2015