PRODUCT INFORMATION

Codral* 4 Flu Tablets

Product description

Each Codral* 4 Flu tablet contains paracetamol 500 mg, codeine phosphate 9.5 mg, pseudoephedrine hydrochloride 30 mg and chlorpheniramine maleate 2 mg.

Codral* 4 Flu tablets also contain: brilliant blue FCF, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate, Compap L, Compap CPM.

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.

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.

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.

Chlorpheniramine maleate is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Chlorpheniramine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 25 to 50% having been reported. About 70% of chlorpheniramine in the circulation is bound to plasma proteins. There is wide inter-individual variation in the pharmacokinetics of chlorpheniramine; half-life values ranging from 2 to 43 hours have been reported. Chlorpheniramine is widely distributed in the body and enters the central nervous system (CNS).

Chlorpheniramine is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorpheniramine. Unchanged drug 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.

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, faster clearance, and a shorter half-life have been reported in children compared to adults.

**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.

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.

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 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.

Chlorpheniramine competes with histamine at central and peripheral histamine$_1$-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release.
Chlorpheniramine is a highly lipophilic molecule that readily crosses the blood-brain barrier.

Chlorpheniramine 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 $\alpha$-adrenergic receptors and blocks cholinergic receptors.

**Indications**

Codral* 4 Flu provides temporary relief of aches, pain, fever, cough, nasal congestion, sneezing, watery eyes, itchy noses and runny noses associated with respiratory tract infections such as colds and flu. Temporary relief of such symptoms may allow rest.

**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).

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).

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.

Chlorpheniramine 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.

Chlorpheniramine 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.

Codeine should be used with caution in patients:
- with decreased respiratory reserve e.g. asthma or COPD
- with pre-existing respiratory depression
- 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 raised intracranial pressure or head injury
- with prostatic hypertrophy
- with hepatic or renal impairment
- with hypotension
- with hypothyroidism.

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.

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

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.
Use with caution in patients with renal or hepatic impairment and in patients with epilepsy.

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 chlorpheniramine. The elderly are more likely to have CNS depressive side effects, including confusion. (See ‘Contraindications’).

**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.

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.

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.

Chlorpheniramine 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.

Trace amounts of codeine are excreted into 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.
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.

Chlorpheniramine 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 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 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 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 chlorpheniramine 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
• Chlorpheniramine when taken concomitantly with phenytoin may cause a decrease in phenytoin elimination.

Adverse reactions

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.

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. These include: cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

Adverse effects of pseudoephedrine include:
• cardiovascular stimulation – elevated blood pressure, tachycardia or arrhythmias
• CNS stimulation – restlessness, insomnia, anxiety, tremors and (rarely) hallucinations
• skin rashes and urinary retention.

Children and the elderly are more likely to experience adverse effects than other age groups.
Central Nervous System (CNS) effects
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.

Anticholinergic effects
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
The recommended dose of Codral* 4 Flu for adults and children over 12 years is two tablets four times a day when necessary.

The maximum dose to be taken in 24 hours is 8 tablets.

Codral* 4 Flu is not recommended for children under 12 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* 4 Flu tablets are pale blue, round and uncoated.
Codral* 4 Flu tablets are available in blister packs of the following sizes:

- 4 tablets (S3) Pharmacist Only Medicine
- 24 tablets*# (S3) Pharmacist Only Medicine

*marketed

Store below 30°C. Store in a dry place, away from direct light.

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Name and Address of Sponsor

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