Product description

PANADOL COLD & FLU RELIEF ORIGINAL FORMULA is a white, capsule-shaped tablet with flat edges, one face marked with C&F, PANADOL on the other.

Ingredients

Active Ingredients:

- Paracetamol - 500 mg

\[
\text{H}_2\text{C} - \overset{\text{O}}{\text{C}} - \overset{\text{NH}}{\text{C}} - \overset{\text{OH}}{\text{C}}
\]

- Pseudoephedrine Hydrochloride - 30 mg

\[
\overset{\text{NHCH}_3}{\text{C}} - \overset{\text{H}_2\text{O}}{\text{C}} - \overset{\text{HCl}}{\text{C}} - \overset{\text{CH}_3}{\text{C}} - \overset{\text{H}}{\text{C}}
\]

- Dextromethorphan Hydrobromide – 15 mg

\[
\overset{\text{H}_3\text{CO}}{\text{C}} - \overset{\text{CH}_3}{\text{N}} - \overset{\text{H}}{\text{C}} - \overset{\text{HBr}}{\text{C}} - \overset{\text{H}_2\text{O}}{\text{C}}
\]
Excipients:
- Talc - purified
- Starch - Maize
- Starch – pregelatinised maize
- Stearic acid
- Povidone
- Sodium benzoate

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 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 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.

Dextromethorphan is well absorbed from the gastrointestinal tract after oral administration. It is metabolised in the liver, exhibiting polymorphic metabolism involving the cytochrome P450 isoenzyme (CYP 2D6). It is excreted in the urine as unchanged dextromethorphan and demethylated metabolites, including dextrorphan, which has some cough suppressant activity. The plasma elimination half-life of dextromethorphan is 1.2 to 3.9 hours. However, the rate of metabolism varies between individuals according to phenotype (extensive v poor metabolisers), with half-life being as long as 45 hours in patients who are poor metabolisers.

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.
PANADOL® COLD & FLU RELIEF ORIGINAL FORMULA TABLETS
PRODUCT INFORMATION

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.

Dextromethorphan is a non-opioid cough suppressant. It is the methylated dextrorotatory analogue of levorphanol, a codeine analogue. Dextromethorphan acts centrally on the cough centre in the medulla and nucleus tractus solaris to increase the cough threshold. It does not have classical analgesic, sedative or respiratory depressant effects at usual antitussive doses.

Indications

PANADOL COLD & FLU RELIEF ORIGINAL FORMULA is used for the fast effective temporary relief of the symptoms of cold & flu.

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);

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.
  • with, or at the risk of developing, respiratory failure (eg those with chronic obstructive airways disease or pneumonia, or during an asthma attack or an exacerbation of asthma)

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

Refer to ‘Interactions with other medicines’ for additional information
Precautions

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

Pseudoephedrine should be used with caution in patients with:
- hypertension
- hyperthyroidism
- diabetes mellitus
- coronary heart disease
- ischaemic heart disease
- raised intra-ocular pressure including glaucoma
- prostatic hypertrophy
- severe hepatic or renal dysfunction.
- epilepsy
- bronchitis
- bronchiectasis
- bronchial asthma

There have been rare cases of posterior reversible encephalopathy (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) reported with sympathomimetic drugs, including pseudoephedrine. Symptoms reported included sudden onset of severe headache, nausea, vomiting and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment. Pseudoephedrine should be discontinued immediately and medical advice sought if signs/symptoms of PRES/RCVS develop.

Dextromethorphan should not be used for chronic persistent cough accompanying a disease state, or for cough associated with excessive secretions.

Dextromethorphan should not be given to patients with or at risk of developing respiratory failure, e.g. asthma, chronic obstructive airways disease, and pneumonia. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. Concomitant use of alcohol should be avoided.

Use with caution in patients taking beta-blockers or other anti-hypertensives, selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants because of the pseudoephedrine content (see Interactions).

Caution should be exercised in patients with mild to moderate kidney impairment and in those with hepatic impairment.
There have been reports of ischaemic colitis with pseudoephedrine. Pseudoephedrine should be discontinued immediately and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Medical advice should be sought if the cough persists, or is accompanied by a high fever, skin rash or persistent headache.

If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

Patients should be advised not to drive or operate machinery if affected by dizziness.

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

**Use in pregnancy**

Pseudoephedrine hydrochloride – 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.

This product should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus.

Paracetamol and dextromethorphan hydrobromide – Category A

Drugs which 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.

**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.

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.

It is not known whether dextromethorphan is excreted in breast milk or whether it has a harmful effect on the breastfeeding infant.

Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.
Interaction 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 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 psycho stimulants – may cause an increase in blood pressure and additive effects
- Pseudoephedrine may antagonise the effect of certain classes of antihypertensives (eg beta blockers, methyl-dopa, reserpine, debrisoquine, guanethidine) see Precautions).
- methyldopa and β-blockers – may cause an increase in blood pressure
- urinary acidifiers enhance elimination of pseudoephedrine
- urinary alkalinisers decrease elimination of pseudoephedrine

Dextromethorphan should not be used in patients taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days. The use of dextromethorphan with, or within two weeks of taking MAOIs, may increase the risk of serious side effects such as hypertensive crisis, hyperpyrexia and convulsions.

Dextromethorphan when used with SSRI’s (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine) may result in a “serotonin syndrome” with changes in mental status, hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor.

Serum levels of dextromethorphan may be increased by the concomitant use of inhibitors of cytochrome P450 2D6, such as the antiarrhythmics quinidine and amiodarone, antidepressants such as fluoxetine and paroxetine, or other drugs which inhibit cytochrome P450 2D6 such as haloperidol and thiouracil.
Concomitant use of dextromethorphan and other CNS depressants (e.g. alcohol, narcotic analgesics and tranquillizers) may increase the CNS depressant effects of these drugs.

**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.

Adverse effects include:
- cardiovascular stimulation – elevated blood pressure, tachycardia or arrhythmias
- central nervous system (CNS) stimulation – restlessness, insomnia, anxiety, tremors and (rarely) hallucinations
- Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome
- urinary retention
- thrombocytopenia
- anaphylaxis
- Bronchospasm in patients sensitive to aspirin and other NSAIDs
- Hepatic dysfunction

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

Adverse effects caused by pseudoephedrine hydrochloride include:
- nervousness, insomnia, agitation, restlessness, hallucinations
- dizziness, tremors
- tachycardia or arrhythmia. Palpitations
- increased blood pressure. Increases in systolic blood pressure have been observed. At therapeutic doses, the effects of pseudoephedrine on blood pressure are not likely to be clinically significant.
- vomiting, dry mouth, nausea
- rash, allergic dermatitis. A variety of allergic skin reactions, with or without systemic features such as bronchospasm and angioedema have been reported following use of pseudoephedrine
- dysuria, urinary retention. Urinary retention is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

Side effects with usual doses of dextromethorphan are uncommon but may include mild drowsiness, fatigue, dystonias, dizziness and gastrointestinal disturbances (nausea or vomiting, stomach discomfort, or constipation).
Side effects that may occur with high doses (overdosage) include excitation, confusion, psychosis, nervousness, irritability, restlessness, “serotonin syndrome”, severe nausea and vomiting, and respiratory depression.

Dosage

**Adults and children 12 years and over:**
2 capsule-shaped tablets (caplets) taken by mouth with fluid every 6 hours as necessary, maximum 8 caplets within 24 hours.

**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.

Do not exceed the stated dose or frequency of dosing.

Minimum dosage interval: 6 hours

Do not use with other paracetamol-containing or decongestant products including cough and cold preparations.

Seek medical advice if symptoms persist for more than 7 days.

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.

**Paracetamol**
Paracetamol overdose may cause liver failure. 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.

**Pseudoephedrine**
Pseudoephedrine overdose may result in symptoms due to central nervous system and cardiovascular stimulation eg excitement, restlessness, hallucinations, hypertension and arrhythmias. In severe cases, psychosis, convulsions, coma and hypertensive crisis may occur. Serum potassium levels may be low due to the extracellular to intracellular shifts in potassium.
Treatment should consist of standard supportive measures. Beta blockers should reverse the cardiovascular complications and the hypokalemia.

**Dextromethorphan**
Dextromethorphan overdose is likely to result in effects similar to those listed under Adverse Reactions. Following large overdoses, additional symptoms may include excitation, mental confusion, restlessness, nervousness and irritability, stupor, ataxia, dystonia, hallucinations, psychosis and respiratory depression.

Supportive and symptomatic care should be provided as required. If overdose is severe, naloxone may be helpful, particularly for patients with respiratory depression.

**Presentation**

*Description:* White capsule-shaped tablets with flat edges, one face marked with PANADOL and C&F on the other

*Pack size:* blister packs of 24

*Poisons Schedule:* S3

Name and address of the sponsor:
GlaxoSmithKline Australia Pty Ltd trading as GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue, Ermington, NSW, Australia 2115

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)
8 July 1991

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