PANADOL® COLD & FLU RELIEF + COUGH CAPLETS

DATA SHEET

Paracetamol (BP) 500mg, Dextromethorphan Hydrobromide (BP) 15mg and Phenylephrine Hydrochloride (BP) 5mg

Presentation

Blue capsule-shaped tablets (caplets) with flat edges, one face is embossed with sun graphic within an oval.

Indications

For the temporary relief of the following symptoms of colds and flu: headache, runny or blocked nose, sore throat, dry cough, body aches and pains. Reduces fever.

Dosage and Administration

Adults and children aged 12 years and over

2 caplets every 4 – 6 hours as necessary. Maximum 8 caplets in 24 hours.
Do not use for more than a few days at a time in adults without medical advice.
Should not be used for more than 48 hours in children aged 12 to 17 except on medical advice.
Do not use in children under 12 years of age.
Do not exceed the stated dose or frequency of dose.

The lowest dose necessary to achieve efficacy should be used.
Should not be used with other paracetamol-containing products, decongestants or cough and cold medicines.
Do not use within several hours of going to bed as it may cause sleeplessness.
Minimum dosing interval: 4 hours

Renal and Hepatic impairment

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. The restrictions related to the use of such combinations in these patients is primarily a consequence of the paracetamol content of the product. (See WARNINGS AND PRECAUTIONS.)
Contraindications

This product is contraindicated in patients:

- with a previous history of hypersensitivity to paracetamol, phenylephrine hydrochloride, dextromethorphan hydrobromide or any of the excipients.
- who are taking, or have taken within the last two weeks, monoamine oxidase inhibitors. (See INTERACTIONS.)
- with, or at risk of developing, respiratory failure (eg those with chronic obstructive airways disease or pneumonia or during an asthma attack or an exacerbation of asthma).

Warnings and precautions

Medical advice should be sought before taking this product in patients with these conditions:

- Chronic or persistent cough such as occurs with asthma and emphysema or where cough is accompanied by excessive secretions.
- Hypertension
- Cardiovascular disease
- Diabetes
- Hyperthyroidism
- Angle closure glaucoma
- Phaeochromocytoma
- An enlargement of the prostate gland
- Occlusive vascular disease (eg Raynaud’s Phenomenon)
- Liver and kidney impairment. Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
- In patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol.

Use with caution in patients taking the following medication:
• Beta-blockers and other antihypertensive drugs
• Tricyclic antidepressants
• Selective serotonin reuptake inhibitors (SSRI) (See INTERACTIONS)

This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants). (See INTERACTIONS.)

Concomitant use of other cough and cold medicines should be avoided.

Concomitant use of alcohol should be avoided (See INTERACTIONS).

Medical advice should be sought if symptoms persist for more than 7 days or are accompanied by high fever, skin rash or persistent headache.

Keep out of sight and reach of children.

Use in Pregnancy

This product should not be used during pregnancy without medical advice.

Phenylephrine - Category B2

Drugs which have 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 show no evidence of an increased occurrence of foetal damage.

Paracetamol and Dextromethorphan – 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.

Paracetamol crosses the placental barrier. Animal studies with paracetamol have not identified any risk to pregnancy or embryo-foetal development.

Use in Lactation

This product should not be used while breastfeeding without medical advice.

Paracetamol is excreted in breast milk. Human studies with paracetamol have not identified any risk to lactation or the breast-fed offspring.
Phenylephrine may be excreted in breast milk.

No relevant data are available for Dextromethorphan.

**Use in children**

Do not give to children under 12 years of age.

**Effects on ability to drive and use machines**

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

**Adverse Effects**

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data.

**Paracetamol**

The frequency of these reactions is unknown but considered likely to be very rare.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm, especially in patients sensitive to aspirin and other NSAIDs</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
</table>
Phenylephrine
The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness, insomnia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Increased blood pressure</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting</td>
</tr>
</tbody>
</table>

Dextromethorphan
The following adverse events have been observed in clinical trials and are likely to represent uncommon adverse reactions to dextromethorphan (i.e. occurring in ≥1/1,000 to 141 <1/100 patients).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Drowsiness, dizziness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disturbance, nausea, vomiting, abdominal discomfort</td>
</tr>
</tbody>
</table>

Post Marketing Experience
Adverse reactions identified during post-marketing use are listed below.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Allergic reactions (eg rash, urticaria, allergic dermatitis)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia, palpitations</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction such as prostatic hypertrophy.</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Serotonin syndrome (with changes in)</td>
</tr>
<tr>
<td>disorders</td>
<td>mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor and hypertension) has been reported when dextromethorphan has been taken concurrently with MAOIs or serotonergic drugs such as SSRIs</td>
</tr>
</tbody>
</table>
## Interactions

Medical advice should be sought before taking paracetamol-phenylephrine-dextromethorphan in combination with these drugs:

<table>
<thead>
<tr>
<th>Medical advice should be sought before taking paracetamol-phenylephrine-dextromethorphan in combination with these drugs:</th>
<th>Severe reactions, including hypertension or serotonin syndrome (see below) may occur when this product is taken concomitantly, or within two weeks of taking an MAOI (see CONTRAINDICATIONS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine oxidase inhibitors (MAOIs)</td>
<td>Concomitant use of dextromethorphan SSRIs, tricyclic antidepressants, or MAOIs may result in serotonin syndrome with changes in mental status, hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor</td>
</tr>
<tr>
<td>Selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants or MAOIs</td>
<td>Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Tricyclic antidepressants (eg amitriptyline)</td>
<td>May increase the risk of cardiovascular side effects with phenylephrine (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Sympathomimetic amines</td>
<td>Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)</td>
<td>Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased. (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Digoxin and cardiac glycosides</td>
<td>Increase the risk of irregular heartbeat or heart attack.</td>
</tr>
<tr>
<td>Warfarin and other coumarins</td>
<td>The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Concomitant use of dextromethorphan and alcohol may increase the CNS depressant effects of both drugs. (See WARNINGS AND PRECAUTIONS.)</td>
</tr>
<tr>
<td>Inhibitors of cytochrome P450 2D6</td>
<td>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 thioridazine.</td>
</tr>
</tbody>
</table>
Overdosage

Symptoms and signs
Paracetamol overdose may cause liver failure which may lead to liver transplant or death.

Phenylephrine overdosage is likely to result in effects similar to those listed under ADVERSE EFFECTS. Additional symptoms may include irritability, restlessness, hypertension and possibly reflux brachycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than required to cause paracetamol-related liver toxicity.

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

Treatment
Immediate medical management is required in the event of an overdose, even if the symptoms of overdose are not present.

If an overdose is taken or suspected, contact the Poisons Information Centre immediately for advice (0800 764 766), or the patient should go to the nearest hospital straight away. This should be done even if they feel well because of the risk of delayed, serious liver damage. (See ADVERSE EFFECTS.)

Administration of N-acetylcysteine may be required.

In cooperative adults, activated charcoal may reduce absorption of the medicine if given within one hour after ingestion.

Treatment of phenylephrine overdosage should be as clinically appropriate. Severe hypertension may need to be treated with an alpha blocking drug such as phentolamine.

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

**Actions**

*Pharmacotherapeutic group:*

Other cold combination preparations.

*Mechanism of action*

**Paracetamol** is a para-aminophenol derivative that exhibits analgesic and antipyretic activity. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

**Phenylephrine hydrochloride** is a sympathomimetic agent with mainly direct effects on adrenergic receptors (predominantly alpha-adrenergic activity) producing nasal decongestion.

**Dextromethorphan** is a non-opioid antitussive used for the relief of coughs, often accompanying colds and respiratory infections. It exerts its antitussive activity by acting on the cough centre of the medulla oblongata, raising the threshold for the cough reflex.

**Pharmacodynamic effects**

The lack of peripheral prostaglandin inhibition by paracetamol confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is, therefore, particularly suitable for patients with a history of disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

**Pharmacokinetics**

**Absorption**

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Food intake delays paracetamol absorption.

Phenylephrine is irregularly absorbed from the gastrointestinal tract.

Dextromethorphan is well absorbed from the gastrointestinal tract.
**Distribution**

Paracetamol is distributed into most body tissues. Binding to the plasma proteins is minimal at therapeutic concentrations but increases with increasing doses.

Due to extensive pre-systemic metabolism by the liver, detailed analysis of the distribution of orally administered dextromethorphan is not possible.

**Metabolism**

Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates.

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 200 mg/kg or 10 g total paracetamol ingested) and, if left untreated, can cause irreversible liver damage.

Phenylephrine is irregularly absorbed from the gastrointestinal tract. It undergoes first-pass metabolism by monoamine oxidases in the gut and liver; orally administered phenylephrine thus has reduced bioavailability.

Dextromethorphan is metabolised in the liver.

**Elimination**

*Paracetamol* is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unmodified paracetamol with 85% to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from one to three hours.

*Phenylephrine* is excreted in the urine almost entirely as the sulphate conjugate. The plasma half-life has been estimated to be 12 to 15 hours.

*Dextromethorphan* is excreted in the urine as demethylated metabolites including dextromethorphan and as a minor proportion of unchanged dextromethorphan. In a small proportion of individuals, metabolism proceeds more slowly and dextromethorphan predominated in blood and urine.
Other

Chemical Structure

**Paracetamol (C₈H₉NO₂)**

![Paracetamol Chemical Structure](image)

**Phenylephrine Hydrochloride (C₉H₁₃NO₂·HCl)**

![Phenylephrine Chemical Structure](image)

**Dextromethorphan Hydrobromide (C₁₈H₂₆BrNO,H₂O)**

![Dextromethorphan Chemical Structure](image)

List of Excipients

- Indigo carmine
- Maize starch
- Microcrystalline cellulose
- Potassium sorbate
- Povidone
- Pregelatinised Maize starch
- Purified talc
- Sodium laurilsulfate
- Stearic acid
Pharmaceutical Precautions

Shelf life
36 months from date of manufacture.

Special storage precautions
Store below 30ºC.

Incompatibilities
Not applicable

Use and handling
No special requirements

Package Quantities

Blister pack of 24 caplets. Each caplet contains 500mg Paracetamol, 15mg Dextromethorphan Hydrobromide and 5mg Phenylephrine Hydrochloride.

Medicine Schedule

Pharmacy Only

Sponsor Details

GlaxoSmithKline Consumer Healthcare,
11th Floor, Zurich House,
21 Queen St
Auckland, New Zealand
Telephone: (09) 367 2970

Auckland, New Zealand Date of Preparation

15 JAN 2016

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