AUSTRALIAN PRODUCT INFORMATION
PANADOL COLD & FLU NIGHT RELIEF PE (PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE, CHLORPHENAMINE MALEATE) TABLETS

1 NAME OF THE MEDICINE
Paracetamol
Phenylephrine Hydrochloride Chlorphenamine Maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredients per tablet:
Paracetamol 500 mg
Phenylephrine hydrochloride 5 mg
Chlorphenamine maleate 2 mg

Excipients with known effect:
Each tablet contains potassium sorbate as preservative

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM
Green capsule-shaped tablets with flat edges.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
For the temporary relief of cold & flu symptoms such as headache, runny or blocked nose, sore throat, body aches and pain to help you rest. Reduces fever.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children aged 12 years and over:

2 tablets at bedtime with water. Maximum 2 tablets in 24 hours.

May cause drowsiness.

Do not use for more than a few days at a time in adults except on medical advice.

Should not be used for more than 48 hours for children aged 12 – 17 except on medical advice.

Do not give to children under 12 years of age.

Do not exceed the stated dose or frequency of dosing.

The lowest dose necessary to achieve efficacy should be used for the shortest duration possible.

Should not be used with other medicines containing paracetamol, phenylephrine, chlorphenamine,

decongestants or antihistamines, including cough and cold medicines.

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 and chlorphenamine content of the product. (**See 4.4 Special warnings and precautions for use**).

4.3 CONTRAINDICATIONS

This product is contraindicated in patients:

- with a previous history of hypersensitivity to paracetamol, phenylephrine, chlorphenamine, other antihistamines or any of the excipients
- with severe hypertension or coronary artery disease
- who are taking Monoamine Oxidase Inhibitors (MAOIs), or who have taken MAOIs within the previous 14 days (**See Section 4.5 Interactions with other medicines and other forms of interactions**) with narrow-angle glaucoma
- with stenosing peptic ulcer
- with symptomatic prostatic hypertrophy
- with bladder neck obstruction
- with pyloroduodenal obstruction
- who are taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants (**See Section 4.5 Interactions with other medicines and other forms of interactions**)
- with, or at risk of developing respiratory failure (e.g. those with chronic obstructive airways disease or pneumonia or during an asthma attack or an exacerbation of asthma).

This product should not be used with other medicines containing paracetamol, phenylephrine, chlorphenamine or other medicines for the relief of colds, congestion or blocked nose.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Contains paracetamol. Do not use with any other paracetamol-containing products, decongestants, antihistamines or cold and flu medicines. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

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 or have sepsis.

Caution should be exercised in patients with kidney impairment. and in those with hepatic impairment due to the paracetamol and chlorpheniramine content of the product. Underlying liver disease increases the risk of paracetamol-related liver damage.

Caution should be exercised in patients with cardiovascular disease, hypertension, hyperthyroidism, prostatic enlargement, diabetes, raised intraocular pressure including glaucoma, phaeochromocytoma, epilepsy, occlusive vascular disease (e.g. Raynaud's phenomenon), bronchitis, bronchiectasis and bronchial asthma.

Caution should be exercised in patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis.

The anticholinergic properties of chlorpheniramine may cause drowsiness, dizziness, blurred vision

and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.

Due to chlorpheniramine content of this product, alcohol should be avoided (**See Section 4.5 Interactions with other medicines and other forms of interactions**).

Concurrent use with drugs which cause sedation, such as anxiolytics and hypnotics may cause an increase in sedative effects, therefore medical advice should be sought before taking this product concurrently with these medicines (**See Section 4.5 Interactions with other medicines and other forms of interactions**).

Children and the elderly are more likely to experience neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness) due to the chlorphenamine content of this product.

Avoid use in elderly patients with confusion.

Use this product with caution in patients taking beta-blockers or other anti-hypertensives, tricyclic antidepressants, digoxin and cardiac glycosides and selective serotonin reuptake inhibitors (SSRI) (**See Section 4.5 Interactions with other medicines and other forms of interactions**).

Due to the phenylephrine content of these products, they should be used with caution in patients taking ergot alkaloids (e.g. ergotamine and methysergide).

This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) (**See Section 4.5 Interactions with other medicines and other forms of interactions**).

Medical Advice should be sought if high fever, skin rash or persistent headache occurs.

If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Paracetamol

The following interactions with paracetamol have been noted:

Coumarins (including warfarin)	Anticoagulant effect may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding. . Anticoagulant dosage may require reduction if treatment with paracetamol containing medication is prolonged.
Substances that increase gastric emptying (eg metoclopramide)	These substances increase paracetamol absorption.
Substances that decrease gastric emptying (eg propantheline, antidepressants with anticholinergic properties, narcotic analgesics)	These substances decrease paracetamol absorption.
Chloramphenicol	Concentrations may be increased by paracetamol

Potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes (eg alcohol, anticonvulsants)	Risk of paracetamol toxicity may be increased.
Probenecid	May affect paracetamol excretion and alter paracetamol plasma concentrations.
Cholestyramine	Reduces the absorption of paracetamol if given within one hour of paracetamol.

Phenylephrine

Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported.

Monoamine oxidase inhibitors	Hypertensive crisis or a serious increase in blood pressure may occur between phenylephrine and monoamine oxidase inhibitors (**See 4.3 Contraindications**).
Sympathomimetic amines such as other decongestants, appetite suppressants and amphetamine-like psychostimulants	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects and other additive effects (**See 4.3 Contraindications**).
Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)	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 4.4 Special warnings and precautions for use**).
Tricyclic antidepressants (eg amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine (**See 4.4 Special warnings and precautions for use**).
Digoxin and cardiac glycosides	Increase the risk of irregular heartbeat or heart attack.
Ergot alkaloids (e.g. ergotamine and methysergide)	Concomitant use of phenylephrine may cause increased risk of ergotism (**See 4.4 Special warnings and precautions for use**).

Chlorphenamine

The following interactions with chlorphenamine have been noted:

Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)	These substances may prolong and intensify the anticholinergic and CNS depressive effects of chlorphenamine. (**See 4.3 Contraindications and 4.4 Special warnings and precautions for use**).
Central nervous system (CNS) depressants	Central nervous system (CNS) depressants (e.g. alcohol, sedatives, opioid analgesics, hypnotics) - may cause an increase in sedation effects (**See 4.4 Special warnings and precautions for use**).
Phenytoin	Chlorphenamine when taken concomitantly with phenytoin may cause a decrease in phenytoin elimination.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data.

Use in pregnancy – Pregnancy 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.

This product should not be used during pregnancy without medical advice. If used, the lowest effective dose and shortest duration of treatment should be considered.

Use in lactation.

This product should not be used whilst breast feeding without medical advice. If used, the lowest effective dose and shortest duration of treatment should be considered.

Paracetamol is excreted in breast milk. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infants.

Phenylephrine may be excreted in breast milk.

Chlorphenamine may inhibit lactation and may be excreted in breast milk.

Use in children
Do not give to children under 12 years of age. Children may experience paradoxical excitation with chlorphenamine.

Use in elderly
The elderly may experience paradoxical excitation with chlorphenamine. The elderly are also more likely to have a central nervous system (CNS) depressive side effects including confusion.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Chlorphenamine may cause dizziness, blurred vision and CNS depressive effects including sedation and impaired performance (impaired driving 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. Patients should be advised not to drive or operate machinery if affected. Due to chlorphenamine content of this product, alcohol should be avoided. (**See Section 4.5 Interactions with other medicines and other forms of interactions**).

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 doses 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.

Body System	Undesirable Effect
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Anaphylaxis, Cutaneous hypersensitivity reactions including among others, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm, especially in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Hepatic dysfunction

Phenylephrine
The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

Body System	Undesirable Effect
Psychiatric disorders	Nervousness
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure, tachycardia or arrhythmias
Gastrointestinal disorders	Nausea, vomiting
Central nervous stimulation	Anxiety

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

Body System	Undesirable Effect	Frequency
Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma (See PRECAUTIONS.)	Rare
Cardiac disorders	Tachycardia, palpitations	Rare
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, allergic dermatitis)	Rare
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction such as prostatic hypertrophy.	Rare
Immune system disorders	Hypersensitivity	Rare

Chlorphenamine
Adverse events that have been observed in historical clinical studies and that are considered to be common or very common are listed below.

Body System	Undesirable Effect	Frequency
Nervous system disorders	Sedation, somnolence Disturbance in attention, abnormal coordination, dizziness, headache	Very common Common

Eye disorders	Blurred vision	Common
Gastrointestinal disorders	Nausea, dry mouth	Common
General disorders and administration site conditions	Fatigue	Common
CNS stimulatory effects	Anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.	Common
Anticholinergic effects	Dryness of the eyes and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia	Common

The frequency of other adverse events identified during post-marketing use is unknown.

Body System	**Undesirable Effect**	**Frequency**
Immune system disorders	Allergic reactions, angioedema, anaphylactic reactions	Unknown
Metabolism and nutritional disorders	Anorexia	Unknown
Psychiatric disorders	Confusion*, excitation*, irritability*, nightmares*	Unknown
Vascular disorders	Hypotension	Unknown
Respiratory, thoracic and mediastinal disorders	Thickening of bronchial secretions	Unknown
Gastrointestinal disorders	Vomiting, abdominal pain, diarrhoea, dyspepsia	Unknown
Skin and subcutaneous disorders	Exfoliative dermatitis, rash, urticaria, photosensitivity	Unknown
Musculoskeletal and connective tissue disorder	Muscle twitching, muscle weakness	Unknown
Renal and urinary disorders	Urinary retention	Unknown
General disorders and administration site conditions	Chest tightness	Unknown

*Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 (13 11 26) 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.

Paracetamol

Symptoms and signs

Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed with hepatic dysfunction and liver toxicity.

Treatment

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

Administration of N-acetylcysteine may be required.

If an overdose is confirmed or suspected, the Poisons Information Centre should be contacted immediately for advice (call 131 126), or the patient should go to a hospital straight away, even if they feel well, because of the risk of delayed, serious liver damage. See Adverse Effects.

Phenylephrine

Symptoms and Signs

Overdose is likely to result in effects similar to those listed under Adverse Effects. Additional symptoms may include irritability, restlessness, hypertension, and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur.

Treatment

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

Chlorphenamine

Symptoms and Signs

Overdose is likely to result in effects similar to those listed under Adverse Effects. Additional symptoms may include paradoxical excitation, toxic psychosis, convulsions, apnoea, dystonic reactions and cardiovascular collapse including arrhythmias.

Treatment

Treatment should be supportive and directed toward specific symptoms. Convulsions and marked CNS stimulation should be treated with parenteral diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. It does not possess anti-inflammatory activity. Paracetamol is thought to produce analgesia through a central inhibition of prostaglandin synthesis.

Phenylephrine acts predominantly by a direct effect on alpha adrenergic receptors. Phenylephrine also has an indirect effect by releasing noradrenaline from its storage sites. Phenylephrine is used as a nasal decongestant to provide symptomatic relief by causing vasoconstriction resulting in redistribution of local blood flow to reduce oedema of the nasal mucosa, thus improving ventilation, drainage and nasal stuffiness.

Chlorphenamine competes with histamine at central and peripheral histamine1-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 histamine1-

receptors but has little effect on histamine2 or histamine3 receptors. Chlorphenamine also activate 5 hydroxytryptamine (serotonin) and α-adrenergic receptors and blocks cholinergic receptors.

Clinical Trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Paracetamol
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Food intake delays paracetamol absorption.
Paracetamol is distributed into most body tissues. Binding to the plasma proteins is minimal at therapeutic concentrations but increases with increasing doses.

Paracetamol is metabolised extensively 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 150 mg/kg or 10 g total paracetamol ingested) and, if left untreated, can cause irreversible liver damage.

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unmodified paracetamol with 85% of a dose of paracetamol is excreted in the urine as free and conjugated paracetamol within 24 hours of ingestion. Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates. The elimination half-life varies from one to three hours.

Phenylephrine Hydrochloride
Phenylephrine is irregularly absorbed from the gastrointestinal tract. Phenylephrine undergoes first-pass metabolism by monoamine oxidases in the gut and liver; orally administered phenylephrine thus has reduced bioavailability.
Phenylephrine undergoes extensive metabolism in the intestinal wall (first pass) and in the liver. The principal routes of metabolism involve sulfate conjugation (primarily in the intestinal wall) and oxidative deamination (by monoamine oxidase); glucuronidation also occurs to a lesser extent.

Phenylephrine undergoes rapid distribution into peripheral tissues. The volume of distribution of phenylephrine is between 200 and 500L, there appears to be minimal brain penetration, and does not seem to cross the placenta and does not appear to be distributed to any great extent in breast milk.

Phenylephrine and its metabolites are excreted mainly in urine. Following oral administration approximately 80% of the dose is excreted in urine within 48 hours principally as metabolites. Approximately 2.5% of an oral dose is excreted in the urine as unchanged drug. The elimination half-life averages 2-3 hours following oral administration.

Chlorphenamine Maleate
Chlorphenamine is absorbed relatively slowly from the gastrointestinal tract with peak plasma concentrations occurring about 2.5 to 6 hours, after oral administration. More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children compared to adults.

Chlorphenamine is widely distributed in the body and enters the CNS.

Chlorphenamine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 25 to 50% having been reported. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide inter-individual variation in the pharmacokinetics of chlorphenamine; half-life values ranging from 2 to 43 hours have been reported. Chlorphenamine maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorphenamine.

Chlorphenamine - 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No Data.

Carcinogenicity
No Data.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: Microcrystalline cellulose, Potassium sorbate, Povidone, Sodium lauryl sulfate, Maize starch, Pregelatinised maize starch, Stearic acid, Purified talc, Brilliant blue FCF, Sunset yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of 24 tablets
Not all packs may be marketed.

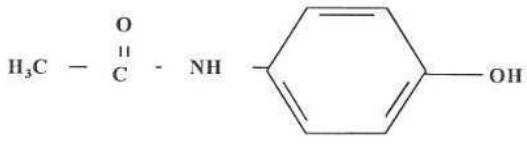
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy

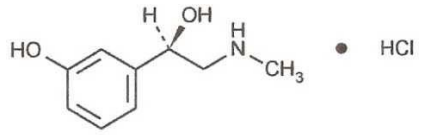
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

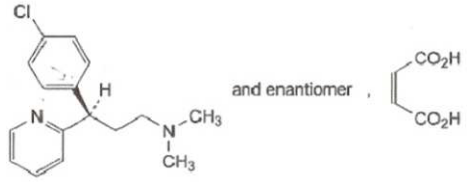
Paracetamol $C_8 H_9 NO_2$



Phenylephrine Hydrochloride $C_9H_{13}NO_2$. HCl



Chlorphenamine Maleate $C_{20}H_{23}ClN_2O_4$.



CAS number
Paracetamol 103-90-2
Phenylephrine hydrochloride 61-76-7
Chlorphenamine maleate 113-92-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 Pharmacy Medicine

8 SPONSOR

GlaxoSmithKline Consumer Healthcare Australia 82 Hughes Avenue
Ermington NSW 2115

Telephone: 02 9684 0888 Website: www.gsk.com.au

9 DATE OF FIRST APPROVAL

14 October 2008

10 DATE OF REVISION

26 May 2021

SUMMARY TABLE OF CHANGES

Section Changed		Summary of new information
All		Reformatted Product Information to new form.
4.2	**Dose and method of administration**	Safety statement shortest duration of treatment.
4.4	**Special warnings and precautions for use**	Additional safety statements, sepsis, use in elderly, cardiac glycosides usage and ergot alkaloids usage.

4.5	**Interaction with other medicines and other forms of interaction**	Additional safety statements in relation to ergot alkaloids.
4.6	**Pregnancy and lactation**	Safety statement around effective dose and shortest duration of treatment. Updated statement for chlorphenamine and lactation.
4.8	**Undesirable effects**	Additional safety statements in relation to Immune System disorders.
4.9	**Overdose**	Safety statement around liver toxicity.