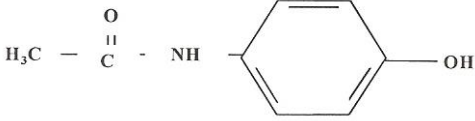
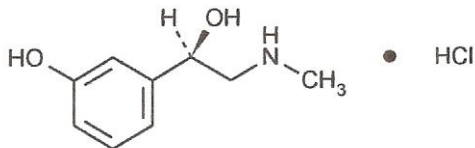
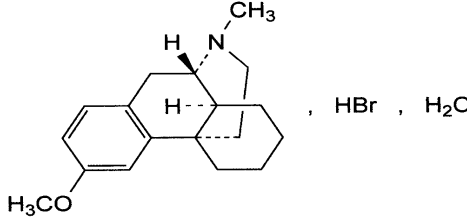
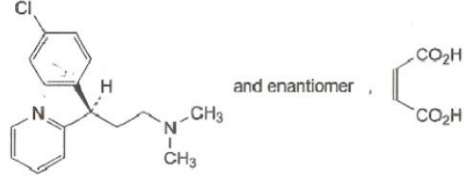


PRODUCT INFORMATION

PANADOL[®] FLU STRENGTH DAY & NIGHT CAPLETS

NAME OF THE MEDICINE

Active ingredients	Chemical structure	CAS Registry Number
Paracetamol		103-90-2
Phenylephrine Hydrochloride		61-76-7
Dextromethorphan Hydrobromide		6700-34-1
Chlorpheniramine Maleate		113-92-8

DESCRIPTION

DAY Caplets - Blue capsule-shaped tablets (caplets) with flat edges, one face is embossed with a ☼ within an oval.

NIGHT Caplets - White capsule-shaped tablets (caplets) with flat edges. One face is embossed with a crescent within an oval.

Formulation

Active Ingredients per caplet:

DAY Caplets - Paracetamol 500 mg, Phenylephrine Hydrochloride 5 mg, Dextromethorphan Hydrobromide 15mg

NIGHT Caplets - Paracetamol 500 mg, Phenylephrine Hydrochloride 5 mg, Dextromethorphan Hydrobromide 15mg, Chlorpheniramine Maleate 2mg

Excipients:

DAY CAPLET	NIGHT CAPLET
Cellulose – microcrystalline	Cellulose - microcrystalline
Potassium sorbate	Potassium Sorbate
Povidone	Povidone
Sodium lauryl sulfate	Sodium Lauryl sulfate
Starch – maize	Starch - Maize
Starch – pregelatinised maize	Starch - pregelatinised maize
Stearic acid	Stearic acid
Talc – purified	Talc - purified
Indigo Carmine	

PHARMACOLOGY

Pharmacodynamics

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.

Chlorpheniramine 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.

Chlorpheniramine also activate 5-hydroxytryptamine (serotonin) and α -adrenergic receptors and blocks cholinergic receptors

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 solitarius to increase the cough threshold. It does not have classical analgesic, sedative or respiratory depressant effects at usual antitussive doses.

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.

Pharmacokinetics

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 inactive 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 overdose (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 unchanged. Approximately 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.

Chlorpheniramine Maleate

Chlorpheniramine 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.

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

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 maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorpheniramine.

Chlorpheniramine - 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.

Dextromethorphan Hydrobromide

Dextromethorphan is well absorbed from the gastrointestinal tract after oral administration.

Dextromethorphan is metabolised in the liver, exhibiting polymorphic metabolism involving the cytochrome P450 isoenzyme (CYP 2D6)..

Dextromethorphan 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.

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.

INDICATIONS

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

CONTRAINDICATIONS

This product is contraindicated in patients:

- with a previous history of hypersensitivity to paracetamol, dextromethorphan, phenylephrine, chlorpheniramine, 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 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 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).
- Who are using other medicines containing paracetamol, phenylephrine, dextromethorphan, chlorpheniramine or other medicines for the relief of coughs & colds, congestion or blocked nose.

PRECAUTIONS

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.

Caution should be exercised in patients with kidney impairment. and in those with hepatic impairment due to the paracetamol, dextromethorphan 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, pheochromocytoma, epilepsy, occlusive vascular disease (e.g. Raynaud's phenomenon), bronchitis, bronchiectasis, bronchial asthma, and in patients with chronic cough, such as occurs with asthma and emphysema, or where cough is accompanied by excessive secretions.

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 and dextromethorphan content of this product, alcohol should be avoided (*see 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 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 chlorpheniramine content of this product.

Use this product with caution in patients taking beta-blockers or other anti-hypertensives, tricyclic antidepressants and 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.

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

If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

Use in pregnancy

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

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.

Use in lactation

This product should not be used whilst breast feeding without medical advice.

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.

Chlorpheniramine is excreted in breast milk.

No relevant data are available for dextromethorphan. It is not known whether dextromethorphan is excreted in breast milk or whether it has a harmful effect on the breastfeeding infant.

Use in children

Do not give to children under 12 years of age.

Children may experience paradoxical excitation with chlorpheniramine.

Use in elderly

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

Effects on ability to drive and use machinery

Chlorpheniramine which is contained in the 'Night' caplets 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 chlorpheniramine and dextromethorphan content of this product, alcohol should be avoided (See INTERACTIONS).

INTERACTIONS WITH OTHER MEDICINES

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 (e.g. metoclopramide)	These substances increase paracetamol absorption.
Substances that decrease gastric emptying (e.g. 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 (e.g. alcohol, anticonvulsants)	Risk of paracetamol toxicity may be increased.
Probenecid	May affect paracetamol excretion and alter paracetamol plasma concentrations.
Colestyramine	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 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 CONTRAINDICATIONS.)
Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyl dopa)	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 PRECAUTIONS.)
Tricyclic antidepressants (e.g. amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine (See PRECAUTIONS.)

	Hypertensive crisis may also occur.
Digoxin and cardiac glycosides	Increase the risk of irregular heartbeat or heart attack.

Chlorpheniramine

The following interactions with chlorpheniramine have been noted:

Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)	These substances may prolong and intensify the anticholinergic and CNS depressive effects of chlorpheniramine. (See CONTRAINDICATIONS and PRECAUTIONS.)
Central nervous system (CNS) depressants (e.g. alcohol, sedatives, opioid analgesics, hypnotics)	Central nervous system (CNS) depressants may cause an increase in sedation effects (See PRECAUTIONS).
Phenytoin	Chlorpheniramine when taken concomitantly with phenytoin may cause a decrease in phenytoin elimination.

Dextromethorphan

The following interactions with dextromethorphan have been noted:

Monoamine oxidase inhibitors (MAOIs)	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.
Selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants	Concomitant use of dextromethorphan with selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine or tricyclic antidepressants such as clomipramine and imipramine, may result in serotonin syndrome with changes in mental status, hypertension, restlessness myoclonus, hyperreflexia, diaphoresis, shivering and tremor (See PRECAUTIONS).
CNS depressants (e.g. alcohol, narcotic analgesics and tranquilizers)	Concomitant use of dextromethorphan and other CNS depressants (e.g. alcohol, narcotic analgesics and tranquilizers) may increase the CNS depressant effects of these drugs. (See PRECAUTIONS.)
Inhibitors of cytochrome P450 2D6	Serum levels of dextromethorphan may be increased by the concomitant use of inhibitors of cytochrome P450 2D6, such as the anti-arrhythmic quinidine and amiodarone, antidepressants such as fluoxetine and paroxetine, or other drugs which inhibit cytochrome P450 2D6 such as haloperidol and thioridazine.

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 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), 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 skin rashes, angioedema and Stevens Johnson syndrome
Respiratory, thoracic and mediastinal disorders	Bronchospasm, especially in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Hepatic dysfunction

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 $\geq 1/1,000$ to $< 1/100$ patients). Adverse reactions are listed below by MedDRA System Organ Class

Body System	Undesirable Effect
Nervous system disorders	Drowsiness, dizziness, fatigue, dystonias
Gastrointestinal disorders	Gastrointestinal disturbance, nausea, vomiting, abdominal discomfort or constipation

Adverse reactions identified during post-marketing use with dextromethorphan are listed below. The frequency of these reactions is unknown but likely to be very rare (occurring in < 1/10,000 patients).

Body System	Undesirable Effect
Immune system disorders	Allergic reactions (e.g. rash, urticaria, angioedema)
Nervous system disorders	Serotonin syndrome (with changes in 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. (see CONTRAINDICATIONS, PRECAUTIONS and INTERACTIONS).

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

Chlorpheniramine

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).

DOSAGE AND ADMINISTRATION

Adults and children aged 12 years and over:

DAY Caplets (Blue): 2 caplets in the morning and in the afternoon taken every 4-6 hours as necessary.

Maximum 4 DAY caplets in 24 hours.

NIGHT Caplets (White): 2 caplets at bedtime with water.

Maximum 2 NIGHT caplets in 24 hours.

The NIGHT caplets may cause drowsiness.

Do not use the DAY caplets within 6 hours of the NIGHT caplets.

This product may cause sleeplessness if taken several hours before going to bed.

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.

Should not be used with other medicines containing paracetamol, dextromethorphan, phenylephrine, chlorpheniramine, 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 chlorpheniramine content of the product. (See PRECAUTIONS.)

OVERDOSAGE

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.

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.

Phenylephrine

Symptoms and Signs

Overdose is likely to result in effects similar to those listed under Adverse Reactions. 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.

Dextromethorphan

Symptoms and Signs

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.

Treatment

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

Chlorpheniramine

Symptoms and Signs

Overdose is likely to result in effects similar to those listed under adverse reactions. 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.

PRESENTATION AND STORAGE CONDITIONS

Blister pack of 24 caplets consisting of 16 DAY caplets & 8 NIGHT caplets

DAY Caplets - Blue capsule-shaped tablets (caplets) with flat edges, one face is embossed with a ☼ within an oval.

NIGHT Caplets - White capsule-shaped tablets (caplets) with flat edges. One face is embossed with a crescent within an oval.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue, Ermington, NSW 2115

POISON SCHEDULE OF THE MEDICINE

S2 - Pharmacy Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

AUST R 148714 04 January 2008

DATE OF THE MOST RECENT AMENDMENT

30 SEP 2015

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