AUSTRALIAN PRODUCT INFORMATION – DEMAZIN® ORIGINAL COLD + FLU RELIEF DAY +NIGHT TABLETS

1 NAME OF THE MEDICINE

Day tablets: Paracetamol and pseudoephedrine hydrochloride

Night tablets: Paracetamol, pseudoephedrine hydrochloride and chlorphenamine maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Day tablet contains:
- Paracetamol 500 mg
- Pseudoephedrine hydrochloride 30 mg

Each Night tablet contains:
- Paracetamol 500 mg
- Pseudoephedrine hydrochloride 30 mg
- Chlorphenamine maleate 2 mg

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablet

Day Tablet: white, round tablet with a break-line.

Night Tablet: pink, round tablet with a break-line.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Temporary relief from the symptoms of colds and flu.

Day Tablet
Temporary relief from the following symptoms: Runny nose, nasal congestion, sinus pain, headache, body aches and pain, and fever.

Night Tablet
Temporary relief from the following symptoms: Runny nose, nasal congestion, headache, pain and fever, and sneezing.

4.2 DOSE AND METHOD OF ADMINISTRATION

This medicine should not be taken with other medicines containing paracetamol unless advised to do so by a doctor or pharmacist.

Adults and children over 12 years:

Day Tablet: Two tablets morning and afternoon if necessary.

Night Tablet: Two tablets at bedtime if necessary. Maximum 6 Day and 2 Night tablets in 24 hours.

Use in adults

Keep to the recommended dose. This medicine should not be taken for more than a few days at a time except on medical advice.

Use in children and adolescents

Not recommended for children under 12 years of age.
Keep to the recommended dose. This medicine should not be taken for more than 48 hours except on medical advice.

4.3 CONTRAINDICATIONS

DEMAZIN Original Cold + Flu Relief Day + Night Tablets is contraindicated for use in patients with the following conditions:

- Known hypersensitivity or idiosyncratic reaction to paracetamol, pseudoephedrine, chlorphenamine (or substances of a similar chemical structure) or any of the other ingredients in this medicine
- Severe hypertension or coronary artery disease
- Taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days
- Narrow-angle glaucoma
- Stenosing peptic ulcer
- Symptomatic prostatic hypertrophy
- Bladder neck obstruction
- Pyloroduodenal obstruction
- Lactating women.

For additional information see section 4.5 Interactions with other Medicines and other forms of Interactions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Use with caution in patients with the following conditions:

- Hypertension
- Hyperthyroidism
- Diabetes mellitus
- Coronary heart disease
- Ischaemic heart disease
- Glaucoma
- Prostatic hypertrophy
- Epilepsy.

This medicine contains pseudoephedrine which may cause sleeplessness if taken up to several hours before going to bed.

Ischaemic colitis

Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued, and medical advice sought if abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

For additional information see section 4.5 Interactions with other Medicines and other forms of Interactions and section 4.7 Effects on ability to drive and use machines.

Use in hepatic impairment

Use with caution in patients with impaired hepatic function.

Use in renal impairment

Use with caution in patients with impaired renal function.

Use in the elderly

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

Paediatric use

Not recommended for children under 12 years of age.
This medicine should not be taken for more than 48 hours except on medical advice see section 4.2 Dosage and Administration.

Children may experience paradoxical excitation with chlorphenamine.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 e.g. 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 chlorphenamine have been noted:
- Central nervous system (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
- When taken concomitantly with phenytoin may cause a decrease in phenytoin elimination.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy 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.

DEMAZIN Original Cold + Flu Relief Day + Night Tablets should not be used in pregnancy unless the potential benefits to the patient are weighed against the possible risk to the foetus.

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. 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.

Chlorphenamine is excreted in breast milk.

Therefore, DEMAZIN Original Cold + Flu Relief Day + Night Tablets is not recommended for breastfeeding mothers (see section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Chlorphenamine 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 of pseudoephedrine include:

- cardiovascular stimulation – elevated blood pressure, tachycardia or arrhythmias
- central nervous system (CNS) stimulation – restlessness, insomnia, anxiety, tremors and (rarely) hallucinations
- skin rashes and urinary retention
- ischaemic colitis (frequency unknown).

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

CNS depressive effects of chlorphenamine 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 chlorphenamine may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of chlorphenamine may cause nervousness, tremor, insomnia, agitation, and irritability.

Side effects of chlorphenamine associated with cholinergic blockage include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.

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

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (tel. 13 11 26) for advice or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

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.

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 histamine$_1$-receptors but has little effect on histamine$_2$ or histamine$_3$ receptors. Chlorphenamine also activates 5-hydroxytryptamine (serotonin) and α-adrenergic receptors and blocks cholinergic receptors.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration.

Pseudoephedrine is readily absorbed from the gastrointestinal tract.

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Bioavailability is low, values of 25 to 50% having been reported. 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 has been reported in children compared to adults.

Distribution

Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses.

Small amounts of pseudoephedrine are distributed into breast milk.

Chlorphenamine is widely distributed in the body and enters the CNS. About 70% of chlorphenamine in circulation is bound to plasma proteins.

Metabolism

Paracetamol is metabolised extensively in the liver. 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.

Pseudoephedrine is incompletely metabolised (less than 1%) in the liver to an inactive metabolite by N-demethylation.

Chlorphenamine maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorphenamine. Chlorphenamine appears to undergo considerable first-pass metabolism.

Excretion

Paracetamol is excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged. The elimination half-life varies from about 1 to 3 hours.

Pseudoephedrine 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.

Unchanged chlorphenamine 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. There is wide inter-individual variation in the pharmacokinetics of chlorphenamine; half-life values ranging from 2 to 43 hours have been reported. Faster clearance and a shorter half-life have been reported in children compared to adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Contains:

- Crospovidone
- Erythrosine aluminium lake (Night tablets only)
- Magnesium stearate
- Microcrystalline cellulose
- Povidone
- Pregelatinised maize starch
- Stearic acid

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

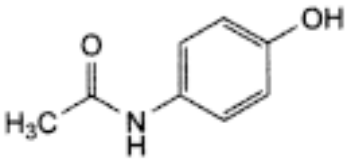
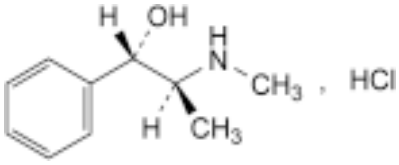
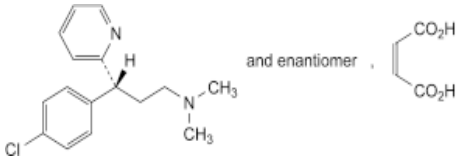
Blister pack - PVC/PVDC/Aluminium foil.
Pack size: 24 tablets. containing 16 white day tablets and 8 pink night tablets.

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 (Day & Night Tablets)	Pseudoephedrine hydrochloride (Day & Night Tablets)	Chlorphenamine maleate (Night Tablets Only)
		
Molecular Formula: $C_8H_9NO_2$ Molecular Weight: 151.2	Molecular Formula: $C_{10}H_{16}ClNO$ Molecular Weight: 201.7	Molecular Formula: $C_{20}H_{23}ClN_2O_4$ Molecular Weight: 390.9

Paracetamol is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Pseudoephedrine hydrochloride is a white or almost white crystalline powder or colourless crystals. It is freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride. Its melting point is at about 184°C.

Chlorphenamine maleate is a white or almost white, crystalline powder. It is freely soluble in water and soluble in ethanol (96 per cent).

CAS number

Paracetamol: 103-90-2

Pseudoephedrine hydrochloride: 345-78-8

Chlorphenamine maleate: 113-92-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacist Only Medicine (S3)

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited
Level 10, 12 Help Street
Chatswood NSW 2067
Telephone toll free 1800 630 056

9 DATE OF FIRST APPROVAL

22 Feb 2017

10 DATE OF REVISION

16 January 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat to new TGA Product Information specifications
4.4	Addition of precaution and adverse effect for ischæmic colitis
8	Change in sponsor
All	Change in name to DEMAZIN Original Cold + Flu Relief Day + Night