# NEW ZEALAND DATA SHEET

# 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

Indicated for temporary relief from the symptoms of cold and flu: runny nose, nasal congestion, headache, body aches and pains, and fever. The night tablets also provide relief from sneezing and itchy or watery eyes and assist rest by providing relief from these symptoms.

### 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.

Do not halve the tablet.

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.
- Uncontrolled hypertension or severe 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.

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.

Effects on sleep
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.

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. Discontinue the product and seek medical advice if abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Serious skin reactions
Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens -Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and use of the product should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Posterior reversible encephalopathy (PRES)/reversible cerebral vasoconstriction syndrome
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. This product should be discontinued immediately, and medical advice sought if signs/symptoms of PRES/RCVS develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine. The product should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

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

No data available.

### 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.
- High anion gap metabolic acidosis from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of paracetamol and flucloxacillin. Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition.

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.
- Antihypertensives e.g. methyldopa and beta-blockers – pseudoephedrine may antagonise the effect of certain classes of antihypertensives and 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.

## 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.

## 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)

Adverse drug reactions identified during post-marketing experience are detailed in the table below.

Additionally, the following should be noted:

- Adverse effects of pseudoephedrine include elevated blood pressure.
- Children and the elderly are more likely to experience adverse effects than other age groups.
- Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Adverse reactions with chlorphenamine:

- 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.

Adverse drug reactions identified during post-marketing experience with paracetamol, pseudoephedrine, and the combination appear in the following table. The frequency category was estimated from spontaneous reporting rates.

Adverse events that have been observed during clinical trials and/or post-marketing use are ranked under the following frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1,000), very rare (<1/10,000).

| ***System Organ Class***<br>Frequency Category | <br>Adverse Event Preferred Term |
|---|---|
| **Blood and lymphatic system disorders** | |
| Unknown | Thrombocytopenia, Agranulocytosis |
| **Immune System Disorders** | |
| Very rare | Anaphylactic reaction, Hypersensitivity |
| **Psychiatric Disorders** | |
| Very rare | Anxiety, Euphoric mood, Restlessness, Insomnia, Hallucinations, Hallucination, visual |
| **Nervous System Disorders** | |
| Very rare | Cerebrovascular accident*, Headache, Paraesthesia, Psychomotor hyperactivity (in the paediatric |

| | |
|---|---|
| | population), Tremor, Posterior Reversible Encephalopathy Syndrome,<br>Reversible Cerebral Vasoconstriction Syndrome |
| **Eye disorders** | |
| Unknown | Ischaemic optic neuropathy |
| **Cardiac Disorders** | |
| Very rare | Arrhythmia, Myocardial infarction*, Palpitations, Tachycardia |
| **Gastrointestinal Disorders** | |
| Very rare | Abdominal discomfort, Colitis ischaemic, Diarrhoea, Vomiting |
| **Skin and Subcutaneous Tissue Disorders** | |
| Very rare | Pruritus, Acute generalised exanthematous pustulosis, Angioedema, Pruritic rash, Rash, Urticaria, Fixed eruption |
| **Renal and Urinary Disorders** | |
| Very rare | Dysuria, Urinary retention |
| **General disorders and administration site conditions** | |
| Very rare | Feeling jittery, Anxiety |
| **Investigations** | |
| Very rare | Blood pressure increased, Transaminases increased |

* These events have been reported very rarely in post-marketing safety. A recent post-authorisation safety study (PASS) did not provide any evidence of increased risk of myocardial infarction or cerebrovascular accident associated with the use of vasoconstrictors for nasal decongestion, including pseudoephedrine.

### Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

## 4.9 OVERDOSE

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)

# 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

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

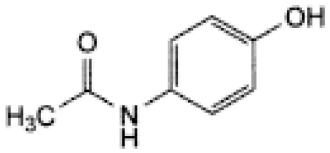
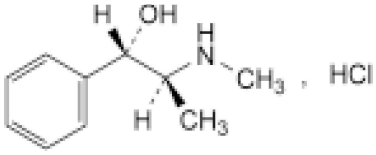
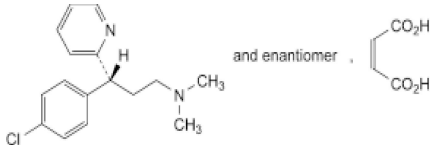
Blister pack - PVC/PVDC/Aluminium foil.
Pack size: 24 tablets containing 16 white day tablets and 8 pink night tablets.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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: $C_8H_9NO_2$<br>Molecular Weight: 151.2 | Molecular Formula: $C_{10}H_{16}ClNO$<br>Molecular Weight: 201.7 | Molecular Formula: $C_{20}H_{23}ClN_2O_4$<br>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$^{o}$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

## 8 SPONSOR

iNova Pharmaceuticals (New Zealand) Limited
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# 9 DATE OF FIRST APPROVAL

12 April 2024

# 10 DATE OF REVISION

10 April 2024

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| All | New data sheet |