

# **PANADOL Night**

***Paracetamol and Diphenhydramine hydrochloride caplets.***

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## **Presentation**

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A film coated, blue caplet (capsule shaped tablet) "PANADOL" printed on one face "NIGHT" on the other.

Each tablet contains 500 mg of paracetamol, 25 mg of diphenhydramine hydrochloride and the following excipient ingredients:

Starch - maize, opadry blue, potassium sorbate, povidone, talc - purified, starch - pregelatinised maize, stearic acid

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## **Uses**

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### ***Actions***

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. The mechanism of action is believed to include inhibition of prostaglandin synthesis. It possesses a weak anti-inflammatory activity. It provides relief from mild to moderate pain and fever.

Diphenhydramine hydrochloride is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of histamine at the H<sub>1</sub> receptor sites. It has additional sedative anticholinergic (antimuscarinic) and local anaesthetic properties.

### ***Pharmacokinetics***

After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma levels occur 10 to 60 minutes after administration.

Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45 to 55%) or sulfate (20 to 30%). A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant. Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85 to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 3 hours. Food intake delays paracetamol absorption.

Diphenhydramine is well absorbed from the gastrointestinal tract following oral administration. It is subject to high first pass metabolism. Peak plasma concentrations are achieved 1 to 4 hours after administration and the effects are maintained for 4 to 6 hours. It is widely distributed throughout the body including the CNS and is highly plasma protein bound. Diphenhydramine is metabolised extensively by the liver and is excreted mainly as metabolites in the urine. Excretion is largely complete within 24 hours of administration.

Pharmacokinetic studies have also been conducted on the combination of paracetamol and diphenhydramine. The bioavailability of paracetamol from the combination product was shown to be similar to the bioavailability of paracetamol from PANADOL tablets.

The  $C_{max}$  and  $AUC_{(0-t_n)}$  of the diphenhydramine component of the combination product were slightly higher than from diphenhydramine tablets. The differences were small but statistically significant. It is possible that the higher levels of diphenhydramine noted for the combination tablets may reflect competition between paracetamol and diphenhydramine for oxidative enzymes.

The  $T_{max}$  values for paracetamol from the combination product were slightly higher than  $T_{max}$  from PANADOL tablets but the difference was not considered statistically significant. This suggests that the presence of diphenhydramine impacts minimally on the rate of gastric emptying at the recommended dose.

### ***Indications***

For the temporary relief of pain when associated with sleeping difficulty; for example, headache, migraine, backache, arthritis, rheumatic and muscle pain, neuralgia, toothache or period pain.

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## **Dosage and Administration**

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Adults and children over 12 years: take 2 tablets with water or other fluid only at bedtime.

A subsequent requirement for analgesia throughout the night should be provided by paracetamol alone. Products containing paracetamol may be taken for daytime pain relief but at a reduced maximum dose of 6 tablets in 24 hours. This would include any extra paracetamol taken throughout the night. Dosage of paracetamol should not be repeated more frequently than every 4-6 hours.

Do not take PANADOL Night for more than 3 consecutive nights without consulting your doctor.

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## Contraindications

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Not for use in children 12 years of age and younger.

Hypersensitivity to paracetamol, diphenhydramine hydrochloride or to any of the excipients.

Diphenhydramine is contraindicated for use in patients with:

- Narrow-angle glaucoma
- Stenosing peptic ulcer
- Symptomatic prostatic hypertrophy
- Bladder neck obstruction
- Pyloroduodenal obstruction

Diphenhydramine is contraindicated for use in:

- Newborns or premature infants
- Lactating women
- Patients taking monoamine oxidase inhibitors (MAOIs)

Refer to “Interactions with other medicines” for additional information.

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## Warnings and Precautions

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Paracetamol and diphenhydramine hydrochloride should be used with care in patients with:

- Impaired hepatic function
- Impaired renal function

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.

Caution should be exercised in patients with epilepsy or seizure disorders, myasthenia gravis, prostatic hypertrophy, urinary retention, asthma, bronchitis and chronic obstructive pulmonary disease (COPD).

Diphenhydramine hydrochloride 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.

Do not take for more than 3 days without consulting a doctor. If symptoms persist, medical advice must be sought.

Refer to “Interactions with other medicines” for additional information.

### ***Use in children and the elderly***

Children and the elderly may experience paradoxical excitation with diphenhydramine. The elderly are more likely to have central nervous system (CNS) depressive side effects, including confusion. (See contraindications.)

### ***Use in Pregnancy (Category A)***

Both paracetamol and diphenhydramine 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.

### ***Use in lactation***

PANADOL Night should not be used whilst breast feeding without medical advice.

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.

Diphenhydramine is excreted in breast milk. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

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

PANADOL Night may cause drowsiness, dizziness, blurred vision, cognitive and psychomotor impairment which can seriously affect the patient's ability to drive or operate machinery. If affected, do not drive or operate machinery.

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## **Adverse Effects**

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Reports of adverse reactions to paracetamol are rare but hypersensitivity including skin rash may occur. Although the following adverse reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted: dyspepsia, nausea, allergic and haematological reactions.

Adverse effects of diphenhydramine hydrochloride may include sedation and the antimuscarinic effects of dry mouth, urinary retention, blurred vision, thickened respiratory tract secretions and chest tightness. Other side effects that may occur occasionally are headache, rashes, cross sensitivity to related drugs, photosensitivity, gastrointestinal disturbances and psychomotor impairment. Dystonic reactions to diphenhydramine have been reported. Blood disorders including agranulocytosis, leucopenia, haemolytic anaemia, though rare, have been reported with antihistamines.

Paradoxical stimulation may rarely occur, especially in high doses or in children.

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## Interactions

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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, eg metoclopramide.
- Paracetamol absorption is decreased by substances that decrease gastric emptying, eg 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 diphenhydramine hydrochloride 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.
- Diphenhydramine is an inhibitor of the cytochrome p450 isoenzyme CYP2D6. Therefore, there may be a potential for interaction with drugs that are primarily metabolised by CYP2D6, such as metoprolol and venlafaxine.

Avoid use with other antihistamine-containing preparations including topical preparations and cough and cold medicines.

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## Overdosage

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If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126; in New Zealand call 0800 764 766) for advice, or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Paracetamol overdose may cause liver failure.

Diphenhydramine overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations and ECG changes. Large overdose may cause rhabdomyolysis, convulsions, delirium, toxic psychosis, arrhythmias, coma and cardiovascular collapse.

## ***Treatment***

### Paracetamol

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. Administration of N-acetylcysteine or methionine may be required.

### Diphenhydramine

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

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## **Pharmaceutical Precautions**

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Store below 30°C.

Protect from moisture.

Keep out of reach of children.

Shelf life of the product is 2 years from the date of manufacture.

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## **Medicine Classification**

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Restricted Medicine.

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## **Package Quantities**

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Packs of 20 containing two blisters of 10 caplets.

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## **Further Information**

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There is no further information for PANADOL Night.

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## **Name and Address**

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## **Date of Preparation**

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24 November 2011