NEW ZEALAND DATASHEET
Paracetamol/Diphenhydramine
(paracetamol & diphenhydramine hydrochloride)

1. PRODUCT NAME

Paracetamol/Diphenhydramine 500 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500 mg, diphenhydramine hydrochloride 25 mg.
For the full list of excipients, see Section 6.1 List of excipients

3. PHARMACEUTICAL FORM

Paracetamol and diphenhydramine film coated tablets.
Blue colour, capsule shaped film coated tablet debossed with "PD5" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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. Relief of fever.

4.2 Dose and method of administration

Adults and children over 12 years: Take 2 tablets with water or other fluid only at bedtime. Maximum of two tablets in 24 hours. Do not exceed the stated dose.

Do not use in children under 12 years of age.

Avoid taking other antihistamine containing products. Other products containing paracetamol may be taken during the day, but the total daily dose of paracetamol must not exceed 4,000 mg in any 24 hour period. Allow at least four hours between taking any paracetamol containing product and Paracetamol/diphenhydramine tablets.

For adults, paracetamol should not be taken for more than 3 consecutive days at a time except on medical advice.

For children, paracetamol should not be taken for more than 48 hours except on medical advice.

Do not halve tablet. Dose equivalence when tablet is divided has not been established.

4.3 Contraindications

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

Not for use for anyone with hypersensitivity to paracetamol, diphenhydramine hydrochloride or to any of the excipients.

Diphenhydramine is contraindicated for use in the following:

- Newborns or premature infants
- Lactating women
- Patients taking monoamine oxidase inhibitors (MAOIs)
- Patients with narrow-angle glaucoma
- Patients with stenosing peptic ulcer
- Patients with symptomatic prostatic hypertrophy
- Patients with bladder neck obstruction, and
- Patients with pyloroduodenal obstruction

See section 4.5 – Interactions with other medicines and other forms of interactions for additional information.

4.4 Special warnings and precautions for use

Contains paracetamol. Do not use with any other paracetamol containing products. The concomitant use with other products containing paracetamol may lead to overdose.

In patients with depleted glutathione states such as sepsis the use of paracetamol may increase the risk of metabolic acidosis.

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.

Keep out of sight and reach of children. Use with caution with:

- drugs with antimuscarinic properties, e.g. atropine, tricyclic antidepressants. See section 4.5 – Interactions with other medicines and other forms of interactions**.**

Use in hepatic impairment
Paracetamol and diphenhydramine hydrochloride should be used with care in patients with impaired hepatic 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.

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 delpleted glutathione levels, such as those who are severely malnourished, anorexic have a low body mass index or are chromic heavy users of alcohol.

Use in renal impairment
Paracetamol and diphenhydramine hydrochloride should be used with care in patients with impaired renal function.

Use in the elderly
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 section 4.3 Contraindications)

Paediatric population
Children may experience paradoxical excitation with diphenhydramine.
Paracetamol/diphenhydramine must not be used use in children under 12 years of age.

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.

Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics

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.

The following interactions with Diphenhydramine have been noted

Anticholinergics – concurrent use of Diphenhydramine with anticholinergic agents may increase the risk of severe constipation and/or urinary retention

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.

4.6 Fertility, pregnancy and lactation

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.

This product is not to be used during pregnancy without medical advice.

Use of sedating antihistamines during the third trimester may result in reactions in the newborn or premature neonates.

Use in lactation.

Paracetamol/diphenhydramine tablets should not be used whilst breastfeeding. 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.

4.7 Effects on ability to drive and use machines

Paracetamol/diphenhydramine tablets 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.

4.8 Undesirable effects

Paracetamol. 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 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 dose and considered attributable are listed below by system organ class and frequency.
As the adverse reactions identified from post-marketing use are reported voluntarily from a population of uncertain size, the frequency is not known but likely to be very rare.

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 in patients sensitive to aspirin and other NSAIDs.
Hepatobiliary disorders. Hepatic dysfunction.

Diphenhydramine. Adverse reactions that have been observed in clinical trials and which are considered to be common or very common are listed below. The frequency of other adverse reactions identified during post-marketing use is not known but these reactions are likely to be uncommon or rare
Central nervous system (CNS) effects. CNS depressive effects of diphenhydramine hydrochloride 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 diphenhydramine may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.
High doses of diphenhydramine may cause nervousness, tremor, insomnia, agitation and irritability.

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

General disorders and administration site conditions. Common (1/10-1/100): fatigue.
Immune system disorders. Not known: hypersensitivity reaction including rash, urticaria, dyspnoea and angioedema.
Psychiatric disorders. Not known: confusion, paradoxical excitation (e.g. increased energy, restlessness, nervousness).
The elderly are more prone to confusion and paradoxical excitation.
Nervous system disorders. Common (1/10-1/100): sedation, drowsiness, disturbance in attention, unsteadiness, dizziness. Not known: convulsions, headache, paraesthesia, dyskinesias.
Eye disorders. Not known: blurred vision.
Cardiac disorders. Not known: tachycardia, palpitations.
Respiratory, thoracic and mediastinal disorders. Not known: thickening of bronchial secretions.
Gastrointestinal disorders. Common (1/10-1/100): dry mouth. Not known: gastrointestinal disturbance including nausea, vomiting.
Musculoskeletal and connective tissue disorders. Not known: muscle twitching.
Renal and urinary disorders. Not known: urinary difficulty, urinary retention.

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
http://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126 or in New Zealand 0800 764766) 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 which can lead to liver transplant or death.

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.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Paracetamol. 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.

The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is, therefore, particularly suitable for patients with a history of disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride competes with histamine at central and peripheral histamine -receptor sites, preventing the histamine$_1$-receptor interaction and subsequent mediator release.

Diphenhydramine is a highly lipophilic molecule that readily crosses the blood brain barrier.

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

Diphenhydramine is effective in reducing sleep onset (i.e. time to fall asleep) and increasing the depth and quality of sleep.

Clinical efficacy and safety

No data available

5.2 Pharmacokinetic properties

Paracetamol

Absorption

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

Distribution

Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. The elimination half-life varies from about 1 to 3 hours.

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.

Excretion

Paracetamol is excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged.

Diphenhydramine hydrochloride.

Absorption

Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. The sedative effect also appears to be maximal within 1-3 hours after administration of a single dose. It is positively correlated with the plasma drug concentration.

Distribution

Diphenhydramine is widely distributed throughout the body, including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly (approx. 80-85%) bound to plasma proteins.

Metabolism

Metabolism is extensive, mainly in the liver. Multiple cytochrome P450 enzymes contribute to the metabolism of diphenhydramine, including CYP2D6. The drug is metabolised principally to diphenylmetoxyacetic acid and is also dealkylated. It undergoes first-pass metabolism in the liver

and only about 40-60% of an oral dose reaches systematic circulation as unchanged diphenhydramine.

Excretion

The metabolites are conjugated with glycine and glutamine and excreted in urine. Diphenhydramine is excreted mainly in the urine as metabolites; little (about 1%) is excreted as unchanged substance. The elimination half-life has been reported to range from 2.4 to 9.3 hours in healthy adults. The terminal elimination half-life is prolonged in liver cirrhosis.

5.3 Preclinical safety data

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Maize starch, potassium sorbate, povidone, croscarmellose sodium, purified talc, stearic acid, Opadry complete film coating system 03F505035 Blue.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25°C. Protect from light. Protect from moisture.

6.5 Nature and contents of container

PVC/Al blister packs of 4, 10, 12 or 20 tablets.

Note: Not all pack sizes may beavailable.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Restricted Medicines

8. SPONSOR

Neo Pharma Limited

Auckland, New Zealand
Contact number: +64 3 4779 669

9. DATE OF FIRST APPROVAL

3 September, 2020

10.DATE OF REVISION

28 September, 2020

Summary table of changes

Section changed	Summary of new information
8	Change in sponsor name