NEW ZEALAND DATA SHEET

Combolieve Night Pain Relief

Film-coated tablets

(Paracetamol, Diphenhydramine hydrochloride)

1 NAME OF THE MEDICINE

Combolieve Night Pain Relief

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500 mg and diphenhydramine hydrochloride 25 mg.

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

3 PHARMCEUTICAL FORM

Combolieve Night Pain Relief is a light blue coloured, film coated caplet plain on both 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 1 - 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 Combolieve Night Pain Relief tablet.

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 exceed the stated dose.

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

To be taken at bedtime.

Should not be used with other anti-histamine containing preparations, including those used on the skin (see Section 4.4 Special warnings and precautions for use).

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Keep out of sight and reach of children.

4.3 CONTRAINDICATIONS

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)

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Contains paracetamol. Do not use with any other paracetamol- containing products. 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.

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.

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

Avoid concurrent use with alcohol, as diphenhydramine may increase the sedative effects of alcohol. Therefore, alcohol should be avoided (see Section 4.5 Interactions with other medicines and other forms of interactions).

Avoid use in elderly patient with confusion. Use with caution in the elderly, who are more likely to experience adverse effects.

Medical advice should be sought before taking in patients with:

- Hepatic or renal impairment. Underlying liver disease increases the risk of paracetamol-related liver damage.
- Glutathione depleted states as the sue of paracetamol may increase the metabolic acidosis.
- Concurrent use of drugs which cause sedation such as tranquilizers, hypnotics and anxiolytics as diphenhydramine may cause an increase in sedative effects (see Section 4.5 Interactions with other medicines and other forms of interactions).

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).

Use with caution with

- Patients with epilepsy or seizure disorders, myasthenia gravis, narrow-angle glaucoma, prostatic hypertrophy, urinary retention, asthma, bronchitis and chronic obstructive pulmonary disease (CPOD), moderate to severe hepatic impairment and moderate to severe renal impairment.
- Monoamine oxidase inhibitors (MAOIs) or within 2 weeks of stopping an MAOI.
- Drugs with antimuscarinic properties e.g. atropine, tricyclics antidepressants

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

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.

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

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

High Anion Gap Metabolic Acidosis

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as the underlying cause of HAGMA in patients with multiple risk factors.

Use in hepatic impairment

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

Use in renal impairment

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

Use in 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). This medicine should not be taken by elderly patients with confusion and paradoxical excitation in the elderly.

Paediatric use

Children may experience paradoxical excitation with diphenhydramine.

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:

- The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding. Anticoagulant dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Diphenhydramine may potentiate the sedative effects of alcohol and other CNS depressants (e.g. codeine, tranquilizers, hypnotics and anxiolytics) and other antihistamines (see Section 4.4 Special warning and precautions for use).
- Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).
- 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.
- As diphenhydramine has some anticholinergic activity, the effects of some anticholinergic drugs may be potentiated. This may result in tachycardia, dry mouth, blurred vision, gastrointestinal disturbances, urinary retention and headaches (see Section 4.4 Special warnings and precautions for use).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Pregnancy category A

Both paracetamol and diphenhydramine have been taken by a large number of pregnant 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 should not be used during pregnancy without medical advice.

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

Use in lactation

Combolieve Night Pain Relief 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Combolieve Night Pain Relief 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 ADVERSE EFFECTS (UNDESIREABLE 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 tabulated 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.

Table 1: Paracetamol post marketing data

Body system	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema and Stevens Johnson syndrome and Toxic Epidermal Necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Hepatic dysfunction

High anion gap metabolic acidosis with frequency "Not known": Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4).

Diphenhydramine

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.

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.

Table 2: Diphenhydramine post marketing data

Body system	**Undesirable effect**
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 & 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 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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

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.

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 histamine1-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release.

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

Diphenhydramine is highly selective for histamine1-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 trails

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Paracetamol

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

Diphenhydramine hydrochloride

Diphenhydramine hydrochloride is well absorbed from the gastro-intestinal 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

Paracetamol

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

Diphenhydramine hydrochloride

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

Paracetamol

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. 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, new-borns, infants and young children compared to adults, the sulphate conjugate being predominant.

Diphenhydramine hydrochloride

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 systemic circulation as unchanged diphenhydramine. The metabolites are conjugated with glycine and glutamine and excreted in urine.

Excretion

Paracetamol

The elimination half-life varies from about 1 to 3 hours.

Diphenhydramine hydrochloride

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

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize starch, microcrystalline cellulose, povidone, talc, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, colouring material (Wincoat WT-AQ-01736 Blue)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Combolieve Night Pain Relief tablets are available in blister packs. The blister packs are packed in a carton. Packs of 8, 10, 16, 20 and 24 tablets are available. All pack sizes may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In New Zealand, any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Pharmacist only medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.

Auckland

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

17 August 2023

10 DATE OF REVISION

August 2025

Summary table of changes

Section changed	Summary of new information
4.4, 4.5, 4.8	Safety update related to High Anion Gap Metabolic Acidosis