NEW ZEALAND DATA SHEET

PARACETAMOL + CODEINE

1. Product Name

Paracetamol + Codeine, 500 mg + 8 mg, tablets.

2. Qualitative and Quantitative Composition

Each Paracetamol + Codeine contains 500 mg of paracetamol and 8 mg of codeine phosphate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Paracetamol + Codeine tablets are round white bevel edged tablets, 13 mm in diameter and 4 mm thick, with MYL on one side and P above the breakline and C below the breakline on the other side.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

For adults and children aged 12 years and above for effective, temporary relief of pain and discomfort associated with:

- headache
- migraine headache
- tension headache
- period pain
- back pain
- muscle pain
- arthritis
- toothache
- dental procedures
- neuralgia
- sore throat
- cold and flu symptoms in adults only (18 years and older)

Paracetamol + Codeine tablets also help reduce fever.

Paracetamol + Codeine is suitable for asthmatics sensitive to aspirin and NSAIDs.

4.2 Dose and method of administration

Dose

Adults and children over 12 years:

1 to 2 tablets every 4 - 6 hours as required. Maximum of 8 tablets in 24 hours.

4.3 Contraindications

Use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol, codeine, other opiates or any of the excipients listed in section 6.1.

In children aged less than 12 years old.

Paracetamol + Codeine is also contraindicated for use in patients:

- with severe hepatic insufficiency
- with acute respiratory depression
- with chronic constipation
- during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate
- who are breastfeeding
- with active alcoholism
- with diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea).
- who are known to be CYP2D6 ultra-rapid metabolisers
- aged below 18 years of age who have undergone tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory adverse reactions.
- aged below 18 years old in whom respiratory function might be compromised (see section 4.4)
- aged below 18 years old for the symptomatic treatment of cough and or cold (see section 4.4)

Also refer to section 4.5.

4.4 Special warnings and precautions for use

Paracetamol + Codeine should be used with caution in patients with:

- decreased respiratory reserve e.g. asthma or chronic obstructive pulmonary disease (COPD)
- pre-existing respiratory depression
- raised intracranial pressure or head injury
- prostatic hypertrophy
- hypotension
- hypothyroidism
- adrenocortical insufficiency

It should also be used with caution in patients who:

- have a history of drug abuse
- are taking other respiratory depressants or sedatives, including alcohol
- have had recent gastrointestinal tract surgery

Paracetamol + Codeine should be used with the utmost caution and in reduced doses in patients with:

- severely impaired kidney function
- impaired liver function or alcoholism

Codeine may obscure the diagnosis or the course of gastrointestinal diseases. Prolonged use of codeine may produce physical and psychological dependence.

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH – medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal.

Concomitant use with benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Paracetamol + Codeine with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see section 4.5).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Paracetamol + Codeine is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of

the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see section 4.5).

Special populations

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and or/adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children and adolescents with compromised respiratory function

Codeine is not recommended for use in children and adolescents aged less than 18 years in whom respiratory function might be compromised, including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Elderly

The elderly are more likely to have age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

Effects on laboratory tests

Plasma amylase and lipase activity
Codeine may cause increased biliary tract pressure, thus increasing plasma amylase and/or lipase concentrations.

Gastric emptying studies
Gastric emptying is delayed by codeine so gastric emptying studies will not be valid.

4.5 Interaction with other medicines and other forms of interaction

Salicylates and NSAIDs

Prolonged concurrent use of paracetamol and salicylates or non-steroidal anti-inflammatory drugs may increase the risk of adverse renal effects.

Coumarins

Concomitant use of warfarin (and other coumarin anticoagulants) and paracetamol may increase the risk of bleeding.

Chloramphenicol

Paracetamol may slow down the excretion of chloramphenicol, entailing the risk of increased toxicity.

Diflusinal

Diflunisal may increase the plasma concentrations of paracetamol by 50%.

Anticholinergics

Concomitant use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention. Drugs, which decrease gastric emptying, may decrease the absorption of paracetamol.

Cholestyramine

Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration.

Propantheline

Decreases gastric emptying which may decrease the absorption of paracetamol.

Rifampicin

Concomitant use may increase the likelihood of paracetamol toxicity.

Alcohol

Increased risk of hepatotoxicity (paracetamol) and risk of sedation (codeine).

Metoclopramide and domperidone

Metacloperamide and domperidone may increase the absorption rate of paracetamol.

Opioid analgesics

Concurrent use of codeine and other opioid agonists is usually inappropriate as additive CNS depression, respiratory depressant and hypotensive effects may occur. Narcotic analgesics may decrease gastric emptying and therefore decrease the absorption of paracetamol.

Barbituates, anxiolytics, hypnotics and anaesthetics

Codeine may potentiate the effects of these drugs. Concomitant use of tranquillisers or sedatives may enhance the potential respiratory depressant effects of codeine.

Barbiturates and antiepileptic medications

The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol, barbiturates or antiepileptic drugs. Phenytoin reduces the bioavailability of paracetamol.

Zidovudine

When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of Paracetamol + Codeine and zidovudine should be avoided. If chronic paracetamol and ziduvodine are to be given concurrently, monitor white blood cell count and liver function tests, especially in malnourished patients.

Antiperistaltic antidiarrhoeals (including kaolin, pectin, loperamide)

Concurrent use of these agents with codeine may increase the risk of severe constipation**.**

Monoamine oxidase inhibitors

Non-selective MAOI's intensify the effects of opioid drugs, which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAOI's or within 10 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAOI's (Reversible Inhibitors of Monoamine Oxidase A) and codeine, caution is advised with this drug combination.

Antihypertensives

Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.

Neuromuscular blocking agents

Codeine may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Cimetidine

Inhibits the metabolism of opioid analgesics.

Benzodiazepines and other CNS depressants

Clinical impact: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Intervention: Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4).

Examples: Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A

Caution should be exercised since codeine metabolites cross the placenta.

Respiratory depression has been reported in neonates in connection with use of codeine during childbirth.

Abstinence symptoms have been reported in babies born to mothers who have regularly used paracetamol/codeine during pregnancy.

Breast-feeding

Paracetamol + Codeine is contraindicated in women during breast-feeding.

At normal therapeutic doses codeine and its active metabolite may be present in breast milk as very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Codeine may cause drowsiness. Those affected should not drive or operate machinery. See section 4.5 for additional information.

4.8 Undesirable effects

Reports of adverse reactions are rare. Although the following reactions have been reported when paracetamol and codeine have been administered:

Haematologic:

Less frequent to rare: agranulocytosis, anaemia, thrombocytopenia.

Genitourinary:

Less frequent to rare: renal failure, uraemia, urinary retention or hesitance.

Hypersensitive:

Less frequent to rare: skin rashes and other allergic reactions, histamine release (hypotension, flushing of the face, tachycardia, breathlessness).

Gastrointestinal:

Common: constipation, nausea, vomiting.
Uncommon: dryness of the mouth.

Neurological:

Common: drowsiness, dizziness, headache.
Less frequent to rare: euphoria, dysphoria, at higher doses codeine may cause respiratory depression.

Hepatic:

Rare: hepatotoxicity, liver damage which may lead to liver failure.
Very rare: pancreatitis

Eye disorders:

Uncommon: disturbances of vision.

Psychiatric disorders:

Rare: sleep disturbances.

Paracetamol has also been associated with dyspepsia, sweating, angioneurotic oedema, leukopenia, agranulocytosis and pancytopenia.

Fatigue may occur commonly.

Very rare cases of serious skin reactions have been reported.

Bronchospasms may be triggered in patients having a tendency of analgesic asthma.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Symptoms of paracetamol poisoning within the first 24 hours after administration are pallor, nausea, vomiting, anorexia and abdominal pain.

Doses over approximately 7.5 to 10 g pose a risk of liver damage. Abnormal glucose metabolism and metabolic acidosis may occur.

In serious cases, hepatic insufficiency may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even without severe liver damage.

Cardiac arrhythmias have also been reported.

Codeine poisoning induces drowsiness, respiratory depression, and finally, coma.

Treatment

Immediate hospitalization.

If the patient has taken approximately 7.5 g or more over the last 4 hours, emptying of the patient's stomach should be undertaken.

IV administration of antidote N-acetylcysteine should be undertaken as soon as possible after administration.

Acetylcysteine 20% intravenously: Administer 20% acetylcysteine immediately without waiting for positive urine test or plasma level results: initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in 500 ml 5% glucose over 4 hours and 100 mg/kg in 1L 5% glucose over 16 hours.

N-acetylcysteine may, however, afford a certain degree of protection even after 10 and up to 48 hours after administration.

In the case of acute codeine poisoning, the treatment is symptomatic. The antidote is naloxone. When treatment for paracetamol toxicity has been initiated; naloxone 400 microgram may be administered SC, IM or IV; IV may be repeated at intervals of 2 to 3 minutes if necessary.

Assisted respiration may be required.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, ATC code: N02AJ06

Mechanism of action

Analgesic and antipyretic

Paracetamol's analgesic mechanism of action has not been fully elucidated but may involve blocking impulse generation at the bradykinin-sensitive chemoreceptors that evoke pain.

The antipyretic effect of paracetamol rises from its ability to block the action of prostaglandin synthetase and so prevent the synthesis of prostaglandins in response to the pyrogen stimulus in the region of the anterior hypothalamus.

Codeine acts centrally. It has an analgesic effect, which is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine.

There is evidence to suggest that a combination of paracetamol with codeine is superior in analgesic action to either drug administered alone.

5.2 Pharmacokinetic properties

Absorption

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 minutes after administration.

Codeine has about one-sixth of morphine's analgesic activity. It is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption.

Distribution

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 milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Biotransformation

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). 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. Patients who metabolise drugs poorly via CYP2D6 (about 8%) are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine.

Codeine is metabolised in the liver to morphine and norcodeine, which with codeine, are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours.

Elimination

Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 4 hours. Food intake delays paracetamol absorption.

6. Pharmaceutical Particulars

6.1 List of excipients

Each tablet contains 500 mg of paracetamol and 8 mg of codeine.

The tablets also contain maize starch, pregelatinised starch, potassium sorbate, povidone, purified talc and stearic acid.

Paracetamol + codeine tablets do not contain lactose, sucrose, gluten, tartrazine or any azo dyes.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Blister packs of 100 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
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Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

18 June 2009

10. Date of Revision of the Text

26 April 2018

Section	
4.1	Removed indication for children under 12 years. Updated indication for cold and flu symptoms for adults only.
4.2	Removed dosage for children under 12 years.
4.3	New contraindications added.
4.4	Minor updates to special population to align with contraindication.