New Zealand Data Sheet

1 PRODUCT NAME CODALGIN TABLETS

Paracetamol 500 mg, Codeine Phosphate 8 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codalgin tablets contain the following Active ingredients – Paracetamol 500 mg, codeine phosphate hemihydrate 8 mg.
It also contains the following Inactives - gelatin, magnesium stearate, microcrystalline cellulose, purified talc, wheat starch

3 PHARMACEUTICAL FORM

Tablet - 12.7mm round, flat bevelled edge, white, with a break-bar on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the temporary relief of pain and discomfort associated with migraine, earache, period pain and rheumatic pain. Reduces fever.

4.2 Dose and method of administration

Adults and children over 12 years: One to two tablets to be taken every four to six hours as necessary. The maximum dosage of tablets in 24 hours is 8 tablets.

Children 7 - 12 years: Half to one tablet to be taken every four to six hours as necessary. The maximum dosage of tablets in 24 hours is 4 doses.

Codalgin should not be given to children under 7 years of age.

4.3 Contraindications

- Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion predisposes patients to paracetamol hepatotoxicity.
- Paracetamol should not be used in patients with a history of intolerance to the drug.
- Codeine should not be used in cases of acute respiratory depression (e.g., acute asthma, acute exacerbations of chronic obstructive pulmonary disease) since codeine may exacerbate the condition.
- Codalgin should not be used in patients with a past history of allergic reactions to codeine.
- Hypersensitivity to any of the tablet excipients.
- Due to codeine's structural similarity to morphine and oxycodone, patients experiencing systemic allergy (generalised rash, shortness of breath) to these drugs should not receive codeine.
- Codeine is contraindicated in patients with diarrhoea caused by poisoning, until the toxic substance has been eliminated from the gastrointestinal tract, or diarrhoea associated with pseudomembranous colitis caused by antibiotic administration since codeine may slow the elimination of the toxic material or antibiotic.

4.4 Special warnings and precautions for use

Warnings and Precautions
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of CODALGIN 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 Interactions with other medicines and other forms of interaction]. 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 CODALGIN 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 Interactions with other medicines and other forms of interaction].

Codalgin should be given with care to patients with impaired renal or hepatic function, viral hepatitis, and to patients taking other drugs which affect the liver. In view of the increased risk of hepatotoxicity, the benefit should be weighed against the risk when administering Codalgin to patients with viral hepatitis or pre-existing hepatic disease. In such patients, hepatic function determinations may be required at periodic intervals during high dose or long-term therapy.

Codeine should be used with caution in patients with a history of drug abuse or with recent gastrointestinal tract surgery.

Codalgin may cause drowsiness. Those affected should not drive or operate machinery.

Physical and/or psychological dependence may occur with the repeated administration of codeine. Tolerance may also result following repeated administration.

Codeine should be administered with great caution in patients with head injury, brain tumour or increased intracranial pressure since codeine may increase the risk of respiratory depression and further elevate intracranial pressure. In addition codeine can produce side effects such as confusion, miosis and vomiting which are important signs in following the clinical course of patients with head injuries.

Codeine should be administered with great caution in patients with decreased respiratory reserve (e.g. in emphysema, kyphoscoliosis, hypoxia, hypercapnia or even severe obesity) or cor pulmonale, or chronic obstructive pulmonary disease since codeine may exacerbate respiratory impairment.

Codeine should be administered with great caution if at all in patients with CNS depression, since codeine may exacerbate the condition.

Codeine should be used with caution in elderly or debilitated patients because of the danger of respiratory or cardiac depression.

Codeine should be administered with caution in patients with acute abdominal conditions since codeine may obscure the diagnosis or the course of the disease.

Codeine should be administered with caution in patients with severe inflammatory bowel disease (risk of toxic megacolon may be increased, especially with repeated dosing).

Codeine should be administered with caution in patients with hypothyroidism, adrenocortical insufficiency (e.g. Addison’s disease), shock, myxedema, acute alcohol intoxication or delirium tremens since codeine may exacerbate the symptoms or increase the risk of respiratory and/or CNS depression.
Codeine should be administered with caution in patients taking Monoamine Oxidase Inhibitors (MAOI’s) – see Interactions with Other Drugs.

Codeine should be administered with caution in patients with a history of convulsive disorders (convulsions may be induced or exacerbated by codeine).

Codeine should be administered with caution in patients with prostatic hypertrophy, urethral stricture or recent urinary tract surgery since codeine may cause urinary retention.

**Use in Children:**

Codalgin can be given in reduced doses to children 7 years and over (see Dosage and Administration). This medication is not suitable for children under 7 years of age.

**Use in the 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.

**4.5 Interaction with other medicines and other forms of interaction**

*Benzodiazepines and other Central Nervous System (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 Warnings and Precautions].

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

*Salicylates and NSAIDs:*

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

*Diflunisal:*

Diflunisal may increase the plasma concentrations of paracetamol by 50%.
**General anaesthetics:**
Codeine may potentiate the effects of general anaesthetics.

**Tranquillisers, sedatives and hypnotics:**
Codeine may potentiate the effects of these drugs.

**CNS depressants:**
Codeine may potentiate the effects of CNS depressants.

**Alcohol:**
Codeine may potentiate the effects of alcohol and the likelihood of toxicity may be increased by its concomitant use. The likelihood of toxicity may also be increased by the concomitant use of alcohol with 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. Opioid agonists that decrease gastric emptying will decrease the absorption of paracetamol.

**Anticholinergics:**
Concomitant use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention. Anticholinergics that decrease the gastric emptying such as propantheline, will decrease the absorption of paracetamol.

**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 14 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAO I’s (Reversible Inhibitors of Monoamine Oxidase A) and codeine, caution is advised with this drug combination. The absorption of paracetamol is decreased by MAO inhibitors that decrease gastric emptying.

**Barbiturates and antiepileptic medications:**
The likelihood of toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol, barbiturates or anti epileptic drugs.

**Coumarins:**
Repeated high doses of paracetamol increase the anti coagulant response to coumarins.

**Chloramphenicol:**
Paracetamol may also increase chloramphenicol concentrations.

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

**Antiperistaltic antidiarrhoals (including kaolin, pectin, loperamide):**
Concurrent use of these agents with codeine may increase the risk of severe constipation.
Metoclopramide:
Drugs that increase gastric emptying such as metoclopramide, may accelerate the absorption of paracetamol. Codeine may antagonise the effects of metoclopramide on gastrointestinal motility.

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

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

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.

4.6 Fertility, pregnancy and lactation

Carcinogenicity, Mutagenicity, Impairment of Fertility:
Clinical toxicity studies in animals have shown that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis; the relevance of this finding to use in humans is not known.

Use in Pregnancy: Category A
Paracetamol crosses the placenta, however problems in humans have not been documented. Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. Administration of codeine during labour may cause respiratory depression in the newborn infant.

Use in Lactation:
Paracetamol is excreted in breast milk but neither paracetamol nor its metabolites were detected in the urine of nursing infants after 650 mg maternal dose. Codeine does pass into breast milk so it should be avoided in breastfeeding women. Codalgin tablets should not be administered while breast-feeding.
4.7 Effects on ability to drive and use machines

Codalgin may cause drowsiness. Those affected should not drive or operate machinery.

4.8 Undesirable effects

Adverse effects of Codalgin tablets are generally infrequent and include:

**Haematologic**

*Less frequent to rare*
- Agranulocytosis
- Anaemia
- Thrombocytopenia

**Genitourinary**

*Less frequent to rare*
- Renal failure
- Uraemia
- Urinary retention or hesitancy

**Hypersensitivity**

*Less frequent to rare*
- Skin rashes and other allergic reactions
- Histamine release (hypotension, flushing of the face, tachycardia, breathlessness)

**Gastrointestinal**

*Common*
- Constipation
- Nausea
- Vomiting

**Neurological**

*Common*
- Drowsiness
- Dizziness

*Less frequent to rare*
- Euphoria, dysphoria
- At higher doses, codeine may cause respiratory depression

4.9 Overdose

Overdosage with Codalgin tablets involves treatment of both paracetamol and codeine poisoning.

**Symptoms:**

**Paracetamol:**
Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and
metabolic acidosis may occur. In severe poisoning, hepatic failure may proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is likely in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite becoming irreversibly bound to liver tissue.

**Codeine:**
Symptoms of codeine overdosage include vomiting, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis, miosis and coma.

**Treatment:**
Contact the Poisons Information Centre on 0800 764 766 immediately.

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### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Actions**

Paracetamol has analgesic and antipyretic activity similar to aspirin. The analgesic effect of paracetamol is thought to be due to inhibition of prostaglandin synthesis in the central nervous system and in the periphery, and, to a lesser extent, by blocking pain impulse generation in the periphery. The antipyretic effect is due to a central action on the hypothalamic heat-regulating centre to produce peripheral vasodilatation and subsequent heat loss.

Codeine phosphate is an opioid analgesic that binds with stereospecific receptors at many sites within the CNS to alter processes affecting both the perceptions of pain and the emotional response to pain. There are multiple sub-types of opioid receptors, each mediating various therapeutic and/or side effects of drugs. Its analgesic effect is thought to be due to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine. Codeine can also cause other effects eg CNS depression, nausea and vomiting, orthostatic hypotension and constipation.

It has been shown that the analgesic effects of paracetamol and codeine are additive due to their different mechanisms of action.

#### 5.2 Pharmacokinetic properties

**Absorption:**

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring some 30 minutes to 2 hours after ingestion.
The onset of therapeutic action is 30 minutes and the duration of effect is 4 hours.

Codeine is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached one hour after oral administration. Onset of action occurs in 15-30 minutes and analgesia is maintained for 4-6 hours.

**Distribution:**

Paracetamol is rapidly and uniformly distributed into most body tissues. It crosses the placenta and is present in breast milk.

Codeine is rapidly distributed to skeletal muscle, kidneys, liver, gastrointestinal tract, lungs, spleen and brain. It crosses the placenta and is distributed in low levels in breast milk.

**Metabolism:**

Approximately 90-95% of the paracetamol dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite which may accumulate in overdosage is hepatotoxic and possibly nephrotoxic.

Codeine is metabolised mainly in the liver. The major metabolic pathway involves glucuronidation of codeine to codeine-6-glucuronide. Codeine can also undergo O- and N-demethylation catalysed by CYP2D6 and CYP3A4 respectively. About 10% of an administered dose of codeine is converted by O-demethylation to morphine which subsequently undergoes glucuronidation to morphine-3 or morphine-6 glucuronide, or N-demethylation to normorphine. Approximately 5-10% of the Caucasian population cannot convert codeine to morphine as they are deficient in the CYP2D6 enzyme. Codeine is also converted by N-demethylation to norcodeine which subsequently undergoes glucuronidation to norcodeine glucuronide or O-demethylation to normorphine.

**Excretion:**

Approximately 85% of a dose of paracetamol is recovered from the urine within 24 hours after ingestion. About 5% is unchanged, the balance consisting mainly of the glucuronide and sulfate conjugates. The elimination half-life varies from 1 to 4 hours and may be prolonged in acute overdosage, in liver disease, the elderly and the neonate.

Codeine is excreted mainly by the kidneys as its metabolite codeine-6-glucuronide. 5-25% is excreted unchanged and approximately 10% is excreted as unchanged or conjugated morphine. The plasma half-life of codeine is 2-4 hours. Only traces of codeine and its metabolites are found in the faeces.

**5.3 Preclinical safety data**

N/A
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Codalgin contains the following excipients - gelatin, magnesium stearate, microcrystalline cellulose, purified talc, wheat starch.

6.2 Incompatabilities
NA

6.3 Shelf life
Store below 30°C in a dry place.

6.4 Special precautions for storage
Store away from heat and moisture

6.5 Nature and contents of container
Available in blister packs of 50 and 100 tablets

6.6 Special precautions for disposal
NA

7 MEDICINE SCHEDULE
Prescription Medicine

8 SPONSOR
Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
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9 DATE OF FIRST APPROVAL
10 DATE OF REVISION OF THE TEXT

22 June 2017

SUMMARY TABLE OF CHANGES

1. Reformatted old data sheet (2014) into new style format.


3. Added in new interactions text as per MEDSAFE letter of 12 April 2017 concerning - Benzodiazepines and other Central Nervous System (CNS) Depressants.