

Data Sheet

ParaCode Extra

Paracetamol 500 mg and Codeine Phosphate 15 mg Tablets

Presentation

White to off white capsule shaped tablets, plain on one side and a break line on the other side.

Each capsule-shaped tablet contains paracetamol 500 mg and codeine phosphate 15 mg. Other ingredients are potato starch, lactose, povidone, docusate sodium, colloidal anhydrous silica and magnesium stearate.

Uses

Actions

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 produces analgesia by dulling the response to painful stimuli at several loci in the CNS. This causes an alteration in the sensation and affective response of pain.

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

Pharmacokinetics

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 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 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 (45-55%) 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 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate 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.

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. It 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.

Indications

For the temporary relief of pain and discomfort associated with:

- Headache
- Migraine Headache
- Backache
- Toothache/Dental Surgery
- Menstrual Pain
- Muscular Pain

Contraindications

Hypersensitivity to paracetamol, codeine or other ingredients.

It must not be used in patients with known glucose-6-phosphate-dehydrogenase deficiency or preexisting respiratory depression, for example acute asthma, acute exacerbations of chronic obstructive pulmonary disease since codeine may exacerbate the condition.

Paracetamol should not be used in patients with a history of intolerance to the drug.

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.

Paracetamol should not be used in patients with active alcoholism as chronic excessive alcohol ingestion predisposes patients to paracetamol hepatotoxicity.

Warnings and Precautions

ParaCode Extra should be administered with caution to patients with hepatic or renal dysfunction, 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 ParaCode Extra 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 CNS depression or decreased respiratory reserve e.g. in emphysema, kyphoscoliosis, hypoxia, hypercapnia or even severe obesity or corpulmonale, or chronic obstructive pulmonary disease. Codeine may exacerbate respiratory impairment and CNS depression. Codeine should be administered with caution in patients with hypothyroidism, adrenocortical insufficiency (eg 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 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 used with caution in patients with a history of drug abuse. Prolonged use of high doses of codeine may produce dependence. Tolerance may also result following repeated administration.

ParaCode Extra may cause drowsiness and/or dizziness. Due to the preparation's sedative action, impairment of the mental and/or physical abilities required for the performance of potentially hazardous activities may occur. Hence children engaging in bike riding and other hazardous activities should be supervised to avoid potential harm.

Adults should not drive, operate machinery, or drink alcohol whilst taking this medication.

Patients with known analgesic intolerance or known bronchial asthma must only use ParaCode Extra after having consulted a physician (hypersensitivity reactions including bronchospasm possible).

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). ParaCode Extra should also be used with caution in patients who have had recent gastrointestinal tract surgery.

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 structure or recent urinary tract surgery since codeine may cause urinary retention.

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 taking Monoamine Oxidase Inhibitors (MAOIs) - see Interactions with Other Drugs.

Use in Pregnancy

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 should be avoided in breastfeeding women. When ParaCode Extra is administered to a nursing mother, alternative arrangements should be made for feeding the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breast feeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultrarapid metaboliser of codeine.

Breast feeding patients should be told how to recognise signs of high morphine levels in themselves and their babies. For example, in a mother, symptoms include extreme sleepiness and trouble caring for the baby. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Medical advice should be sought immediately.

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.

Carcinogenicity

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.

Interactions

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: Repeated high doses of paracetamol increase the risk of bleeding in patients taking warfarin and other coumarin derivatives. Monitoring of coagulation and bleeding complications is required.

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

Diflunisal: 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: Codeine may potentiate the effects of alcohol and the likelihood of paracetamol toxicity may be increased by its concomitant use.

Metoclopramide: Codeine may antagonise the effects of metoclopramide on gastrointestinal motility. Paracetamol absorption is increased by drugs, which increase gastric emptying.

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.

Tranquillisers, sedatives, hypnotics, General anaesthetics and CNS depressants: Codeine may potentiate the effects of these drugs. Concomitant use of tranquilisers 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 anti epileptic drugs.

Zidovudine: When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of ParaCode Extra and zidovudine should be avoided. If chronic paracetamol and zidovudine 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.

Effect 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.

Adverse 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.

Neurological

Common: drowsiness, dizziness.

Less frequent to rare: euphoria, dysphoria, at higher doses codeine may cause respiratory Depression.

Hepatic

Very rare: pancreatitis

Paracetamol has also been associated with dyspepsia, sweating, angioneurotic oedema, leukopenia, agranulocytosis and pancytopenia. Bronchospasms may be triggered in patients having a tendency of analgesic asthma.

Dosage and Administration

Adults and Children over 12 years

2 tablets every 4-6 hours with water as required (maximum 8 tablets in 24 hours).

Children under 12 years

Not suitable.

Overdosage

Symptoms

Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (30 tablets) of paracetamol; a dose of 25 g (50 tablets) or more is potentially fatal. Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to

develop.

In an evaluation of codeine intoxication in children, symptoms seen included: sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur.

Treatment

Consists primarily of management of paracetamol toxicity; naloxone is the treatment of choice for codeine intoxication. In cases of overdosage, methods of reducing the absorption of ingested drug are important. Prompt administration of 50 g activated charcoal and 500 mL iced mannitol 20% by mouth may reduce absorption.

If the history suggests that 15 g paracetamol or more has been ingested, administer one of the following antidotes:

Acetylcysteine 20% i.v

Administer 20% acetylcysteine (Parvolex, David Bull) 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; or

Oral Methionine

2.5 g immediately followed by three further doses of 2.5 g at four hourly intervals. For a 3-year-old child, 1g methionine 4-hourly for four doses has been used.

If more than ten hours have elapsed since the overdosage was taken, the antidote may be ineffective. 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.

Contact the Poisons Information Centre on **0800 764 766** or **0800 POISON** for advice on the treatment and management of any overdose.

Pharmaceutical Precautions

Shelf life and Special Precautions for Storage

2 years. Store at or below 30°C.

Medicine Classification

Pharmacist Only Medicine

Package Quantities

Available in blister packs of 10, 20, 30 & 40 tablets.

Not all pack sizes may be marketed.

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