PRODUCT INFORMATION

Codagesic

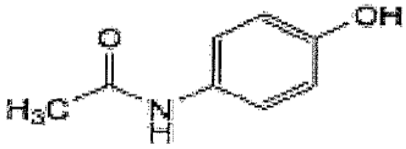
(New Formulation)

Paracetamol, Codeine phosphate hemihydrate and Doxylamine succinate

NAME OF THE MEDICINE

Paracetamol 500mg, Codeine phosphate hemihydrate10mg and Doxylamine succinate 5.1mg

Paracetamol:

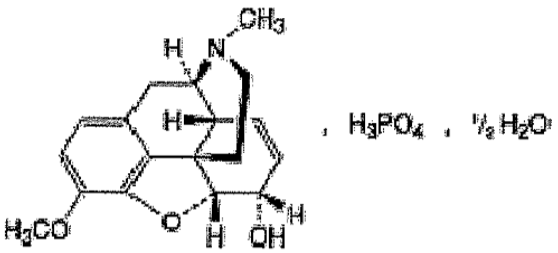


Molecular Formula: $C_8H_9NO_2$.

Molecular weight: 151.2

CAS: 103-90-2.

Codeine phosphate hemihydrate:

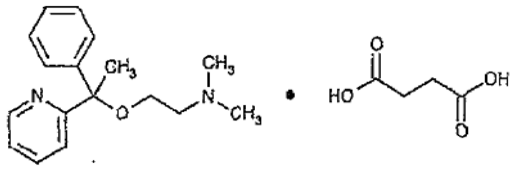


Molecular Formula: $C_{18}H_{21}NO_3$, H_3PO_4, ½ H_2O.

Molecular weight: 406.4

CAS: 1444-62-6

Doxylamine succinate:



Molecular Formula: $C_{17}H_{22}N_2O0.C_4H_6O_4$

Relative Molecular Mass: 388.46

CAS: 562-10-7

DESCRIPTION

Paracetamol is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride. Paracetamol is an analgesic and antipyretic.

Codeine phosphate hemihydrate is a white or almost white, crystalline powder or small, colourless crsytals. It is freely soluble in water, slightly soluble or very slightly soluble in ethanol (96%). Codeine phosphate hemihydrate is a cough suppressant and an analgesic.

Doxylamine succinate is a white or creamy white powder with a characterisitc odour.

Actives: Each tablet contains Paracetamol 500mg Codeine phosphate hemihydrate 10mg and Doxylamine succinate 5.1mg.

Excipients: Lactose monohydrate, Maize starch, Povidone, Ethanol, Crospovidone, Microcrystalline cellulose, Stearic acid, Magnesium stearate.

PHARMACOLOGY

Paracetamol is an effective and fast acting analgesic that relieves mild to moderate pain. It is rapidly absorbed from the gastrointestinal tract with peak plasma levels usually reached 30 to 60 minutes after oral administration. It also reduces fever by a direct effect on the heat regulating centres to increase dissipation of body heat.

Codeine phosphate hemihydrate is an effective oral analgesic that provides relief from mild to moderate pain. It is also well absorbed from the gastrointestinal tract after oral administration.

Doxylamine succinate belongs to the ethanolamine class of antihistamines with sedative properties.

Pharmacokinetics

Paracetamol

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

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulfate 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 conjunction with glutathione, however, it can accumulate following paracetamol overdosage (more than 150mg/kg or 10g total paracetamol ingested) and if left untreated can cause irreversible liver damage.

Paracetamol is metabolized differently by premature infants, newborns, infants and young children compared to adults, the sulfate conjugate being predominant.

Codeine

Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma-codeine concentrations occur at about one hour after ingestion of codeine phosphate hemihydrate. Codeine is metabolized by *O*- and *N*-demethylation and in the liver (via the cytochrome P450 system) to morphine (about 10 per cent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Approximately 3% to 16% of a dose is eliminated unchanged in the urine.

About 8% of people metabolise drugs poorly via CYP2D6, and are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine. The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

Doxylamine succinate

Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration, the mean peak plasma concentration occurs after 2-3 hours. It has an elimination half-life of about 10 hours in healthy adults. It is excreted in the urine as unchanged doxylamine (60%) and metabolites (nordoxylamine and dinordoxylamine).

The major metabolic site is the liver and major metabolic pathways are N-demethylation, N-oxidation, hydroxylation, N-acetylation, N-desalkylation and ether cleavage.

INDICATIONS

For the effective temporary relief of pain and discomfort associated with neck and back pain, headache, tension headache, migraine headache, toothache, muscle pain, neuralgia, arthritis, rheumatics, osteoarthritis, period pain, symptoms of cold and flu, sore throat, trauma, surgery, dental procedures, other pain where a combined calmative and analgesic action is required. Reduces fever.

CONTRAINDICATIONS

Codagesic Tablets are contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol, codeine, doxylamine succinate or substances of similar chemical structure or other opiates or other antihistamines of the ethanolamine class (or any of the other ingredients in the product).

Codagesic Tablets are also contraindicated for use in patients:

- 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
- 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).
- narrow-angle glaucoma
- stenosing peptic ulcer
- symptomatic prostatic hypertrophy
- bladder neck obstruction
- pyloroduodenal obstruction

Codagesic Tablets are contraindicated for use in:

- newborns or premature infants
- lactating women
- patients taking monoamine oxidase inhibitors (MAOIs)

PRECAUTIONS

Products containing codeine should not be given for prolonged periods as codeine may be habit forming. This medication may be dangerous when used in large amounts or for long periods.

Hepatotoxicity may develop following a dose of paracetamol 10g and hepatic failure is known to occur occasionally with the long term use of paracetamol.

Patients should be cautioned against the concomitant ingestion of alcohol and antihistamines.

Codagesic Tablets should be used with caution in patients with:

- impaired hepatic function
- impaired renal function
- epilepsy
- 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

This medicine 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

Codeine present in this medicine may obscure the diagnosis or the course of gastrointestinal diseases.

Codeine present in this medicine may produce physical and psychological dependence, if used for a prolonged period.

Codagesic Tablets 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.

Impaired Renal function

Paracetamol should be given with care to patients with impaired kidney function.

Impaired Hepatic function

Paracetamol should be given with care to patients with impaired liver function.

Use in Pregnancy (Category A)

Paracetamol, Codeine phosphate hemihydrate and Doxylamine succinate have been taken by a large number of pregnant women and women of child bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Use in Lactation

Codagesic Tablet is not recommended for use by breastfeeding mothers as doxylamine, codeine and paracetamol are excreted in breast milk in small amounts.

Effect on Ability to Drive or Operate machinery

Both doxylamine succinate and codeine phosphate hemihydrate may cause drowsiness in some patients; therefore patients should be cautioned about operating vehicles or machinery, or engaging in activities that require them to be fully alert.

INTERACTION WITH OTHER MEDICINES

The following interactions have been noted:

Interactions with Paracetamol:

- *Coumarins:* Repeated high doses of paracetamol increase the risk of bleeding in patients taking warfarin and other coumarin derivatives. Dosage reduction of anticoagulants, monitoring of coagulation and bleeding complications is required.
- *Chloramphenicol:* Paracetamol may slow down the excretion of chloramphenicol, causing the risk of increased toxicity.
- *Cholestyramine:* Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration.
- *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.
- *Probenecid:* Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.
- Concomitant use of paracetamol and isoniazid, phenytoin, zidovudine or sulfinpyrazone has been reported to result in hepatotoxicity. Therefore, patients receiving isoniazid, phenytoin, zidovudine or sulfinpyrazone therapy should avoid large and/or chronic doses of paracetamol.
- *Narcotic analgesics* and drugs, which decrease gastric emptying, may decrease the absorption of paracetamol and vice versa.
- Drugs, which increase gastric emptying, may increase the absorption of paracetamol.

Interactions with Codeine:

- *Anticholinergics:* Concomitant use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention.
- *Neuromuscular blocking agents:* Codeine may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.
- *Antihypertensives:* hypotensive effects may be potentiated when used concurrently with codeine and lead to orthostatic hypotension
- *Antiperistaltic antidiarrhoeals* (e.g. kaolin, pectin and loperamide): their concurrent use with codeine may increase the risk of severe constipation.
- *Alcohol:* Codeine may potentiate the effects of alcohol.
- *Metoclopramide:* codeine may antagonise the effects of metoclopramide on gastrointestinal motility.
- *Monoamine oxidase inhibitors (MAOIs):* concurrent administration or use within 14 days of ceasing MAOIs may enhance the potential respiratory depressant effects of codeine.
- *Opioid analgesics:* concurrent use of codeine and other opioid receptor antagonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur.
- Substances that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.
- Codeine may potentiate the effects of tranquillisers, sedatives, hypnotics, general anaesthetics and CNS depressants.

Interactions with Doxylamine succinate:

- *Monoamine oxidase inhibitors (MAOIs):* concurrent administration or use within 14 days of ceasing MAOIs may enhance or prolong the anticholinergic and CNS depressive effects of doxylamine succinate.

ADVERSE EFFECTS

Side effects with Codagesic Tablets are infrequent. However, among those reported are anorexia, drowsiness, depression, dizziness, gastrointestinal discomfort (e.g. nausea and diarrhoea), dry mouth and, on rare occasions, rash.

Paracetamol may occasionally cause skin reactions, and isolated cases of agranulocytosis and thrombocytopenic purpura have been reported. Doxylamine succinate may cause drowsiness in some individuals. Constipation may occur in association with codeine.

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.

The most common adverse effects associated with codeine are nausea, vomiting, drowsiness, dizziness and constipation.

Other side effects include: cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

Central Nervous Systems (CNS) effects

CNS depressive effects of doxylamine succinate 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 doxylamine succinate may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of doxylamine succinate may cause nervousness, tremor, insomnia, agitation, and irritability.

Anticholinergic effects

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

DOSAGE AND ADMINISTRATION

Adults and children over 12 years: One or two tablets every four to six hours as needed for relief. Do not exceed eight tablets in a 24 hour period. For short term use only. This product is not recommended for use over long periods.

Children under 12 years: Not recommended for use in children under 12 years.

OVERDOSAGE

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766), or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage with paracetamol.

Paracetamol: It has been reported that paracetamol may produce symptoms of acute toxicity in adults following the ingestion of more than 15g. Hepatotoxicity may develop after the ingestion of a single dose of 10 to 15g (200 to 250 mg/kg) and a dose of more than 25g is potentially fatal. Patients may be asymptomatic for several days following ingestion of large doses of paracetamol and laboratory evidence of hepatotoxicity may be delayed for up to one week. Non-fatal hepatic damage is usually reversible. The antidote, N-acetylcysteine, should be administered as early as possible.

Codeine: In an evaluation of codeine intoxication in children, symptoms ranked by decreasing order of frequency included sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur. Blood concentrations of codeine ranged from 1.4 to 5.6 microgram/mL in eight adults whose deaths were attributed primarily to codeine overdosage.

Doxylamine: Reactions associated with doxylamine overdosage may vary from CNS depression to stimulation. Stimulation is particularly likely in children. Insomnia, nervousness, euphoria, irritability, tremors, nightmares,

hallucinations and convulsions can occur. Atropine-like signs and symptoms (e.g. dry mouth, fixed and dilated pupils, flushing and gastrointestinal symptoms) may also occur.

PRESENTATION AND STORAGE CONDITIONS

Codagesic Tablets : White, capsule shaped, biconvex, bevel edged uncoated tablets with break line on one side and plain on other side.

PVC/PVDC/Alu Blister packs of 20 or 40 tablets

Store below 30ºC.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

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30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

POISON SCHEDULE OF THE MEDICINE

S3 (Pharmacist Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

24/03/2015

DATE OF MOST RECENT AMENDMENT

30/11/2016