DATA SHEET

Codeine phosphate tablets

Codeine phosphate as 15 mg, 30 mg and 60 mg tablets.

Presentation

Codeine phosphate 15 mg, 30 mg and 60 mg tablets are white, circular, film-coated tablets embossed with 'DP' on one side and '15', '30' and '60' respectively on the other.

Uses

Actions

Codeine phosphate is an opioid analgesic with uses similar to those of morphine, but is much less potent as an analgesic and has only mild sedative effects. Its primary site of action is at the mu opioid receptors distributed throughout the central nervous system.

Codeine phosphate reduces intestinal motility through both a local and possibly central mechanism of action. Codeine phosphate also suppresses the cough reflex by a direct central action, probably in the medulla or pons.

Codeine and its salts are absorbed from the gastro-intestinal tract and onset of analgesic action occurs 30 to 45 minutes after administration, when given orally.

Peak effect is reached within 1 to 2 hours and the duration of analgesic and antitussive action are 4 hours and 4 to 6 hours respectively.

Pharmacokinetics

Codeine is readily absorbed from the gastro-intestinal tract and metabolised by O- and N-demethylation in the liver to morphine and norcodeine which with codeine are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

Most of the excretion products appear in the urine within 6 hours and 40 to 60 per cent of the codeine is excreted free or conjugated, approximately 5 to 15 per cent as free and conjugated morphine and about 10 to 20 per cent as free and conjugated norcodeine.

Indications

Codeine phosphate is indicated for:

- the relief of mild to moderate pain (including pain associated with terminal illness, post-operative pain and headache),
- the relief of symptoms of diarrhoea (except diarrhoea caused by poisoning),

- as an antitussive in the control of non-productive cough.

Codeine is particularly valuable for pain associated with coughing.

Dosage and administration

Adults

Codeine phosphate may be given orally in doses of 15 mg – 60 mg up to 6 times a day for the relief of pain. If these doses fail to relieve pain, larger doses rarely succeed and may give rise to restlessness and excitement. The maximum recommended daily dose is 300 mg.

For non-productive cough the usual dose is 10 mg – 20 mg every 4-6 hours to a maximum total of 120 mg in 24 hours.

Paediatric

The usual paediatric dose for analgesia in infants and children is 0.5 mg per kg of body weight or 15 mg per square meter of body surface, every 4 to 6 hours as needed.

For cough children may be given up to 0.25 mg per kg every 4 - 6 hours.

On the basis of available data, codeine and other opioid cough suppressants should rarely be administered to children less than 6 to 12 months old. They should not be given in productive cough. When indicated for the treatment of non-productive cough, which interferes with sleep or school attendance, codeine may be recommended in the form of single-ingredient preparations.

Contraindications

- Known hypersensitivity to codeine, other opioids or any component of the tablets
- Acute respiratory depression (especially in the presence of cyanosis and excessive bronchial secretion)
- Obstructive airways disease
- Acute alcoholism
- Head injuries or conditions in which intracranial pressure is raised
- Patients at risk of paralytic ileus
- Hepatic failure
- Acute asthma attack
- Heart failure secondary to chronic lung disease
- Diarrhoea associated with pseudomembranous colitis or diarrhoea caused by poisoning
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

Warnings and precautions

Codeine phosphate should be used with caution in patients with the following conditions:

- Hypothyroidism

- Adrenocortical insufficiency e.g. Addison's Disease
- Impaired kidney/liver function
- Prostatic hypertrophy
- Shock/ hypotension
- Myasthenia gravis
- Convulsions/ convulsive disorders
- Gall bladder disease or gall stones
- Recent gastro-intestinal surgery
- Urinary tract surgery
- Reduced respiratory function or history of asthma
- Obstructive and inflammatory bowel disease – codeine reduces peristasis, increases tone and segmentation in the bowel and can raise colonic pressure.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

Hypersensitivity – Maculopapular rash, fever, splenomegaly and lymphadenopathy have been seen as part of a codeine hypersensitivity reaction.

Dependence – taking codeine regularly for a long time can lead to addiction. Stopping treatment can result in withdrawal symptoms. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for headache can result in an overuse syndrome.

Withdrawal – abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure. These effects can also occur in neonates exposed to codeine in utero (see use in pregnancy).

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Genetic polymorphism – Codeine is metabolised to morphine by cytochrome P450 2D6. Some patients are ultra-rapid metabolisers and are at higher risk of toxic opioid effects. Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

Use in Pregnancy – The balance of benefits and risks should be carefully considered because opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high-dose use of Codeine prior to delivery may produce Codeine withdrawal symptoms in the neonate.

Although teratogenic effects in humans have not been done, studies in animals have not shown codeine to cause adverse effects on foetal development. Studies in animals have shown codeine (single dose of 100 mg per kg) to cause delayed ossification in mice and (in doses of 120 mg per kg) increased resorption in rats.

Use during Lactation - Codeine is excreted into breast milk. However with usual analgesic doses, concentrations are generally low.

However, infants of nursing mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Nursing mothers taking codeine, who are ultra-rapid metabolisers, may have higher morphine levels in their breast milk, which may lead to life-threatening or fatal side effects in nursing babies.

When prescribing codeine for a nursing mother, the lowest dose for the shortest amount of time to relieve pain or cough should be prescribed. Nursing patients should be told how to recognize signs of high morphine levels in themselves and their babies.

Signs of high morphine levels in a mother are extreme sleepiness and trouble caring for the baby.

Breastfed babies usually nurse every two to three hours and should not sleep more than four hours at a time. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice.

Use in children – Children up to 2 years of age may be more susceptible to the effects, especially the respiratory depressant effects of opioid analgesics. Paradoxical excitation is especially likely to occur in paediatric patients receiving these medicines.

Use in the Elderly - Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects, of these medications. Also geriatric patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment, and are therefore more likely to be adversely affected by opioid-induced urinary retention. The risk of constipation and faecal impaction is also greater in the elderly.

Geriatric patients may metabolize or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective for these patients.

Effects on ability to drive and use machines - codeine may cause drowsiness or a decrease in alertness in some patients. Patients should be cautioned about operating vehicles or machinery, or engaging in activities which require them to be fully alert.

Adverse effects

Immune system disorders – rash, urticaria, pruritus, difficulty breathing, increased sweating, redness of flushed face, angioedema

Nervous system disorders – confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental depression, headache, nightmares, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia

Eye Disorders – miosis, blurred or double vision

Cardiac Disorders – bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia

Respiratory, thoracic and mediastinal disorders- respiratory depression

Gastrointestinal Disorders – constipation, biliary spasm, nausea, vomiting, dry mouth

Musculoskeletal, connective tissue and bone disorders – muscle rigidity

Renal and Urinary Disorders – ureteral spasm, anti-diuretic effect, urinary retention

Reproductive system and Breast Disorders- decrease in libido and potency

Withdrawal effects – abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regular prolonged use of codeine is known to lead to addiction and tolerance.
Prolonged used of a painkiller for headaches can make them worse.

Interactions

- Monoamine Oxidase Inhibitors – due to the possible risk of excitation or depression, avoid concomitant use and for 14 days after discontinuation of MAOI
- Alcohol – enhanced sedative and hypotensive effect, increased risk of respiratory depression
- Hypnotics and anxiolytics – enhanced sedative effect, increased risk of respiratory depression
- Anticholinergics – risk of severe constipation which may lead to paralytic ileus and/or urinary retention
- Metoclopramide and domperidone – antagonistic effect on GI activity
- Anti-diarrhoeal drugs – increased risk of severe constipation
- Anaesthetics – enhanced sedative and hypotensive effect
- Tricyclic antidepressants – enhanced sedative effect
- Antipsychotics – enhanced sedative and hypotensive effect
- Opioid antagonists – may precipitate withdrawal symptoms
- Quinidine – reduced analgesic effect
- Antihypertensive drugs – enhanced hypotensive effect
- Ciprofloxacin – avoid premedication with opioids as they reduce ciprofloxacin concentration
- Ritonavir – may increase plasma levels of opioid analgesics

- Mexiletine – delayed absorption of mexiletine
- Cimetidine – inhibits the metabolism of opioid analgesics causing increased plasma codeine concentrations

Overdosage

Symptoms: Poisoning with codeine produces central stimulation and exhilaration and, in children, convulsions, followed by vomiting, drowsiness, respiratory depression and cyanosis, and coma. Death may occur from respiratory failure.

Toxic doses vary considerably with the individual and regular users may tolerate larger doses.

Treatment: The stomach should be emptied by aspiration or lavage. A laxative may be given to aid peristalsis. Intensive supportive therapy may be required to correct respiratory failure and shocks. In addition, the specific antagonist naloxone hydrochoride is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses of opioid analgesics. A dose of 0.4 mg to 2 mg is given intravenously, intramuscularly or subcutaneously, repeated at intervals of 2 to 3 minutes if necessary, up to 10 mg. The effect of naloxone may be of shorter duration than that of the opioid analgesic and additional doses may be required to prevent relapses.

The use of opioid antagonists such as naloxone, nalorphine and levallorphan in persons physically dependant on opioid agonists may induce withdrawal symptoms.

Pharmaceutical precautions

Protect from light and moisture. Store below 30 ºC. Keep out of reach of children.

Medicine classification

Controlled Drug C2.

Package quantities

Codeine 15mg: 100's
Codeine 30mg: 100's
Codeine 60mg: 100's

Further information

Codeine is obtained from opium or made by methylating morphine. It occurs as odourless colourless crystals or white crystalline powder. Codeine phosphate has a molecular formula and weight of $C_{18}H_{21}NO_3$, H_3PO_4, $\frac{1}{2}H_2O$ and 406.37 respectively.

Codeine phosphate tablets distributed by Douglas Pharmaceuticals Ltd are not substitutable with any other brands of codeine phosphate tablets.

Other ingredients of the tablets are: Lactose, Maize Cornflour, microcrystalline cellulose, Sodium Starch Glycolate, Magnesium Stearate, Polyvinylpyrrolidinone K30 and Opadry White Y-1-7000B.

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