

DHC CONTINUS[®]

Dihydrocodeine hydrogen tartrate 60mg tablet

Presentation

Dihydrocodeine hydrogen tartrate Ph Eur in a white, biconvex, capsule-shaped tablet 12mm in length and 5mm width, plain on one side and embossed DHC 60 on the other.

Uses

Actions

Dihydrocodeine is a semi-synthetic narcotic analgesic with potency between morphine and codeine. In mice the ED₅₀ for analgesic effect after s.c. administration was 12.4mg/kg compared to morphine (2.1mg/kg) and codeine (14.2mg/kg). Duration of analgesia was about 2 hours for morphine and dihydrocodeine and about 1 hour for codeine.

Besides analgesia, dihydrocodeine has an antitussive effect (depression of the cough reflex by direct effect on the cough centre in the medulla). Antitussive effects may occur with dosages lower than those usually required for analgesia. Dihydrocodeine also causes a reduction in motility of gastrointestinal smooth muscle with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Dihydrocodeine acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to the pain by reducing the associated anxiety. Unlike morphine, dihydrocodeine is not a full agonist. Increasing the human dose beyond 240mg/day does not produce useful additional analgesic effect.

Through direct action on the central nervous system, dihydrocodeine may also produce drowsiness, mental clouding and mood alteration (euphoria or dysphoria).

Such effects may be common at first but tolerance develops on prolonged administration. Other centrally mediated effects that are normally of low incidence at therapeutic doses include respiratory depression, nausea and vomiting. Respiratory depression results from reduced responsiveness of the respiratory centre to carbon dioxide. Nausea and vomiting are a consequence of direct stimulation of the chemoreceptor trigger zone.

Pharmacokinetics

Dihydrocodeine is well absorbed from the gastrointestinal tract following administration of DHC CONTINUS[®] tablets; however, it is subject to extensive first pass metabolism in the liver. Peak concentrations of 125ng/ml have been measured in healthy volunteers after administration of one 60mg tablet. The time for peak concentration was 3.5h with a range of 2.0-6.0h. Therapeutic plasma levels are maintained throughout the twelve hour dosing interval.

Like other phenanthrene derivatives, dihydrocodeine is mainly metabolised in the liver with resultant metabolites excreted mainly in the urine. The metabolism of dihydrocodeine includes O-demethylation, N-demethylation and 6-keto reduction. The terminal phase rate constant has been measured at 0.173h^{-1} corresponding to terminal phase elimination half-life of 4h.

Absorption and clearance of dihydrocodeine is delayed in the presence of renal insufficiency such that a reduction in dose is recommended. It is also recommended to reduce dosage in the presence of impaired hepatic function.

Indications

DHC CONTINUS[®] tablets are recommended for use in the treatment of post-operative pain, and pain associated with cancer.

DHC CONTINUS[®] tablets are also indicated for the treatment of opioid-responsive, chronic severe pain of non-malignant origin, after other conservative methods of analgesia have been tried. It is indicated for use in accordance with the NZMA guidelines on chronic pain management and where there is no psychological contraindication, medicine-seeking behaviour or history of medicine misuse.

Dosage and Administration

DHC CONTINUS[®] tablets must be swallowed whole and not chewed. The tablets should be taken at twelve hourly intervals at a dose of 60-120mg twice daily depending on the severity of the patient's pain. The maximum recommended dose is 240mg daily since higher doses do not provide any further analgesic effect.

DHC CONTINUS[®] tablets should be administered initially at the lowest dose possible in elderly or debilitated patients, patients with impaired renal function, impaired hepatic function, or hypothyroidism.

Contraindications

Known hypersensitivity to dihydrocodeine or to any of the excipients. Respiratory depression. Obstructive airways disease. As dihydrocodeine may cause the release of histamine it should not be given during an asthma attack. Dihydrocodeine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy as the respiratory depressant effects of dihydrocodeine may be enhanced.

Warnings and Precautions

Head Trauma and Increased Intracranial Pressure

The depressant effects of dihydrocodeine may be exaggerated in the presence of increased intracranial pressure or head injury. In such patients, dihydrocodeine must be used with caution and only if it is judged essential.

Asthma

As dihydrocodeine may cause the release of histamine, it should be given with caution to asthmatics. As dihydrocodeine may cause the release of histamine it should not be given during an asthma attack.

Special Risk Groups

The dosage of dihydrocodeine should be reduced in the elderly, in hypothyroidism, chronic hepatic disease, biliary tract disorder, pancreatitis, impairment of liver function, prostatic hypertrophy, severe renal dysfunction, severe chronic obstructive airways disease, severe cor pulmonale, and renal insufficiency.

Use with caution in patients suffering constipation. DHC CONTINUS[®] tablets should not be used where there is a possibility of paralytic ileus. Should paralytic ileus be suspected or occur during use, DHC CONTINUS[®] tablets should be discontinued immediately.

The prolonged treatment with DHC CONTINUS[®] tablets may potentially affect the reproductive function including menstrual disturbances, decreased libido and infertility.

Tolerance to analgesic effects may develop upon repeated administration.

Use in Pregnancy and Lactation

There is little published evidence on safety in human pregnancy. DHC CONTINUS[®] tablets should be avoided to the extent possible in patients who are pregnant and only be used where the benefit outweighs risk to the foetus.

Dihydrocodeine has not been reported to be excreted in breast milk. However, it is advisable that dihydrocodeine should be avoided to the extent possible and only be administered to breast-feeding mothers if considered essential.

Effects on Ability to Drive and use Machines

Dihydrocodeine may impair the ability of the patient to drive or operate machinery. If so affected, patients should be warned against these activities.

Use in Children

DHC CONTINUS[®] tablets are not recommended for use in children under twelve years of age.

Drug Abuse and Dependence

DHC CONTINUS[®] tablets should be administered with caution in patients with a history of opiate abuse or dependence. Patients may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of DHC CONTINUS[®] may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with DHC CONTINUS[®], it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Dihydrocodeine has a recognized abuse and addiction profile similar to other opioids. Dihydrocodeine may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including dihydrocodeine. Dihydrocodeine should be used with particular care in patients with a history of alcohol and drug abuse.

The controlled release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release tablets leads to a rapid release and absorption of a potentially fatal dose of dihydrocodeine and may result in overdose effects (see **Overdosage**).

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

In patients already habituated to a drug such as pethidine, the substitution of dihydrocodeine in equi-analgesic doses has led to the appearance of abstinence symptoms.

Adverse Effects

The adverse effects listed below are classified by body system according to their incidence (common [≥ 1%] or uncommon [<1%]).

Immune system disorders

Uncommon: angioedema

Psychiatric disorders

Uncommon: confusional state, drug dependence, hallucination, mood altered, dysphoria

Vascular disorders

Uncommon: hypotension

Nervous system disorders

Common: somnolence

Uncommon: convulsions, dizziness, headache, paraesthesia, sedation

Ear and labyrinth disorders

Uncommon: vertigo

Skin and subcutaneous tissue disorders

Uncommon: hyperhidrosis, pruritus, rash, urticaria

Gastrointestinal disorders

Common: abdominal pain, constipation, dry mouth, nausea, vomiting

Uncommon: diarrhoea, paralytic ileus

Hepato-biliary disorders

Uncommon: biliary colic, hepatic enzymes increased

Renal and urinary disorders

Uncommon: urinary retention

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, respiratory depression

General disorders and administration site conditions

Uncommon: asthenic conditions, withdrawal syndrome

Interactions

Dihydrocodeine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, phenothiazines, anxiolytics, anti-depressants, antipsychotics, other tranquilizers and alcohol. Interactive effects may result in respiratory depression or sedation.

Dihydrocodeine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Overdosage

Signs and Symptoms

Acute overdosage with dihydrocodeine is characterised by pin-point pupils; respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis); extreme somnolence progressing to stupor or coma; flaccidity of skeletal muscle; cold or clammy skin, and sometimes hypotension and bradycardia. Continued overdosage may result ultimately in apnoea, circulatory collapse, cardiac arrest and death.

Treatment

Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway, supplemental oxygen and controlled or assisted ventilation.

The narcotic antagonist naloxone hydrochloride is a specific antidote. An appropriate dose of naloxone hydrochloride should, therefore, be administered, preferably by the intravenous route; the usual initial i.v. adult dose is 0.4mg. This may be repeated at 2-3 minute intervals as necessary, or by an infusion of 2mg in 500mL of normal saline or 5% dextrose (0.004mg/mL).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response.

If the tablets are likely to be still in the stomach, gastric lavage should be considered. Maintain fluid balance.

The physician should be aware that DHC CONTINUS[®] tablets remaining in the intestine may continue to release dihydrocodeine for a period of hours.

Overdose can result from the immediate release of dihydrocodeine if the controlled release tablet is chewed or crushed before administration.

Pharmaceutical Precautions

Store below 30°C. Protect from light and moisture. Keep out of reach of children. DHC CONTINUS[®] tablets have a shelf-life of 3 years.

Medicine Classification

Controlled Drug C2.

Package Quantities

60 tablets.

Further Information

Dihydrocodeine hydrogen tartrate is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol hydrogen tartrate. Its molecular formula and weight are $C_{18}H_{23}NO_3C_4H_6O_6$ and 451.5 respectively.

Other ingredients of the tablets are lactose anhydrous, hydroxyethylcellulose, cetostearyl alcohol, magnesium stearate and purified talc.

Toxicity

The Registry of Toxic Effects of Chemical Substances (1981-2) gives the following acute toxicity data for dihydrocodeine.

| Species | Route of Administration | Result |
|----------------|--------------------------------|----------------|
| Rat | Oral | LD50: 240mg/kg |
| Mouse | Subcutaneous | LD50: 225mg/kg |
| Rabbit | Oral | LD50: 400mg/kg |
| Guinea Pig | Subcutaneous | LD50: 80mg/kg |

Name and Address

Sponsor

Mundipharma New Zealand Ltd

Distributor

Pharmaco (NZ) Ltd
P O Box 4079
Auckland
Ph: (09) 377 3336

Date of Preparation

5 July 2011

CCDS June 2011

® DHC CONTINUS and CONTINUS are Registered Trademarks

The Trademark CONTINUS® distinguishes the controlled release preparations of Mundipharma and its associates.