NEW ZEALAND DATA SHEET

DHC CONTINUS® 60mg tablets

Dihydrocodeine hydrogen tartrate

1 PRODUCT NAME

DHC CONTINUS® 60mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dihydrocodeine hydrogen tartrate 60mg equivalent to 40mg dihydrocodeine

Excipient(s) with known effect:

Lactose anhydrous

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets: White, biconvex, capsule-shaped 12mm in length and 5mm wide, plain on one side and embossed DHC 60 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 current guidelines on chronic pain management and where there is no psychological contraindication, medicine-seeking behaviour or history of medicine misuse.

4.2 Dose and method of administration

Adults and children over 12 years of age:

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.

Children 12 years or under:

Not recommended.

Elderly and Special Risk Groups:

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.

Method of administration:

DHC CONTINUS® tablets must be swallowed whole and not broken, chewed or crushed.

4.3 Contraindications

- Known hypersensitivity to dihydrocodeine hydrogen tartate or to any of the excipients (see section 6.1)
- Severe chronic obstructive lung disease
- Severe *cor pulmonale*
- Severe bronchial asthma
- Severe respiratory depression with hypoxia
- DHC CONTINUS® 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

4.4 Special warnings and precautions for use

DHC CONTINUS® tablets should be administered with caution in the elderly or patients with

- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Biliary tract disorders
- Pancreatitis
- Impairment of hepatic function
- Severe renal dysfunction
- Chronic obstructive pulmonary disease
- *Cor pulmonale*
- Bronchial asthma
- Respiratory depression with hypoxia
- Constipation
- Hypothyroidism
- Prostatic hypertrophy
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse (see below)

Respiratory depression

The major risk of opioid excess is respiratory depression*.*

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of the pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

CNS depressants co-administration

Concomitant use of DHC CONTINUS® and sedative medicines such as benzodiazepines or related drugs such as 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) may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe DHC CONTINUS® concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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).

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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when DHC CONTINUS® 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).

MAOIs

DHC CONTINUS® must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

Tolerance, physical dependence and withdrawal

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® tablets 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® tablets, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse

Dihydrocodeine has a recognized abuse and addiction profile similar to other opioids.

There is potential for development of psychological dependence (addiction) to opioids analgesics, including dihydrocodeine. Dihydrocodeine may be sought and abused by people with latent or manifest addiction disorders. Dihydrocodeine should be used with particular care in patients with a history of substance misuse disorder (including alcohol abuse) or mental health disorder.

Parenteral abuse of dosage forms not approved for parenteral administration can be expected to result in serious adverse events, which may be fatal.

Controlled release tablets

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 **section 4.9**).

Use in Children

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

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 DHC CONTINUS® should be reduced in the elderly, in hypothyroidism, chronic hepatic disease, biliary tract disorder, pancreatitis, impairment of hepatic function, prostatic hypertrophy, severe renal dysfunction, severe chronic obstructive airways disease, severe *cor pulmonale*, and renal insufficiency (see section 4.2).

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.

Effects on hypothalamic-pituitary-adrenal or gonadal axes

Opioids, such as dihydrocodeine, may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines and other Central Nervous System (CNS) Depressants:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics, general anaesthetics, gabapentin and sedatives (including benzodiazepines), antipsychotics, and antidepressants, phenothiazines and alcohol.

Co-administration with MAOIs or within two weeks of discontinuation of their use is inappropriate.
Significant impairment of motor function has also been noted following concomitant dihydrocodeine administration and alcohol ingestion.

Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of dihydrocodeine.

Diazepam, when used following high doses of dihydrocodeine hydrogen tartrate, exacerbates the hypotensive effects produced by dihydrocodeine, and is associated with reduced plasma catecholamine levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited 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.

Prolonged use of DHC CONTINUS® during pregnancy can result in neonatal opioid withdrawal syndrome.

Breastfeeding

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. Prolonged use of DHC CONTINUS® during pregnancy can result in neonatal opioid withdrawal syndrome.

Fertility

No human data on the effect of dihydrocodeine on fertility are available (see section 5.3).

4.7 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.

4.8 Undesirable 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 (see section 4.4), hallucination, mood altered, dysphoria

Vascular disorders

Uncommon: hypotension

Nervous system disorders

Common: somnolence

Uncommon: convulsions, dizziness, headache, paraesthesia, sedation

Not known: Sleep apnoea syndrome

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: asthenia, fatigue, malaise, withdrawal syndrome

Not Known: drug withdrawal syndrome neonatal, drug tolerance

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Signs and Symptoms

Acute overdosage with dihydrocodeine can be manifested by somnolence progressing to stupor or coma, miotic pupils, bradycardia, hypotension, rhabdomyolysis and respiratory depression or apnoea, which may – in severe cases – result in a fatal outcome.

Treatment

A patent airway must be maintained. The pure opioid antagonists are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02AA08

Dihyrodrocodeine is an opioid agonist with no antagonistic action.

Central Nervous System

The principal actions of therapeutic value of dihydrocodeine are analgesia and an antitussive effect (depression of the cough reflex by direct effect on the cough centre in the medulla). Antitussive effects may occur with doses lower than those usually required for analgesia.

Dihydrocodeine may produce respiratory depression by direct action on brain stem respiratory centres.

Gastrointestinal Tract and Other Smooth Muscle

Dihydrocodeine causes a reduction in motility associated with an increase in smooth muscle 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.

5.2 Pharmacokinetic properties

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. 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. 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.

5.3 Preclinical safety data

No regulatory studies to assess genotoxicity, carcinogenicity, reproductive or developmental effects of dihydrocodeine have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose, hydroxyethylcellulose, cetostearyl alcohol, magnesium stearate and purified talc

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

60 tablets. Bottles with polypropylene lid and polyethylene body.

6.6 Special precautions for disposal

None.

7 MEDICINE SCHEDULE

Controlled Drug C2.

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
4.3,4.4,4.5,4.8 and 4.9	Administrative/Editorial updates in sections 4.3,4.4,4.5,4.8 and 4.9 Addition of central sleep apnoea and worsening of pre-existing sleep apnoea in section 4.4 Updating of information on fertility in section 4.6 in line with section 5.3 Addition of sleep apnoea syndrome and drug tolerance to undesirable effects in section 4.8