# 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® is indicated for the management of severe pain where:

- other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- the pain is opioid-responsive, and
- requires daily, continuous, long term treatment.

DHC CONTINUS® is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

DHC CONTINUS® is not indicated as an as-needed (PRN) analgesia.

### 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
- Constipation
- Hypothyroidism
- Prostatic hypertrophy
- Sleep apnoea
- CNS depressants co-administration ( 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)

***Hazardous and harmful use***

DHC CONTINUS® contains the opioid dihydrocodeine hydrogen tartrate and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed DHC CONTINUS® at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the

longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed DHC CONTINUS®.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 and section 6.6). Caution patients that abuse oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share DHC CONTINUS® with anyone else.

***Respiratory depression***

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of DHC CONTINUS® but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients. The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of the pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

***Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol***

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of DHC CONTINUS® with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe DHC CONTINUS® concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation.

Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking DHC CONTINUS®.

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).

***Use of opioids in chronic (long-term) non-cancer pain (CNCP)***

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see *Hazardous and harmful use, above*). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period

or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see *Ceasing Opioids*).

***Tolerance, physical dependence and withdrawal***

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing DHC CONTINUS® in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids*).

***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).

***Accidental ingestion/exposure***

Accidental ingestion or exposure of DHC CONTINUS®, especially by children, can result in a fatal overdose of DHC CONTINUS®. Patients and their caregivers should be given information on safe storage and disposal of unused DHC CONTINUS® (see section 6.4 and section 6.6).

***Hyperalgesia***

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

***Ceasing opioids***

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been

taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

***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

Distributed on behalf of Mundipharma New Zealand Limited by:
Pharmaco (N.Z.) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Ph: (09) 377-3336
Toll Free [Medical Enquiries]: 0800 773 310

## 9 DATE OF FIRST APPROVAL

26 March 1992

## 10 DATE OF REVISION OF THE TEXT

18 March 2022

[CCDS 17 Jun 2021, V10.0]

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.1 | Update to indication as per MARC request |