1 PRODUCT NAME
DHC CONTINUS® 60mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Dihydrocodeine hydrogen tartrate 60mg

Excipient(s) with known effect:
Lactose anhydrate.
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 or to any of the excipients.
- Severe chronic obstructive lung disease.
- Severe cor pulmonale.
- Severe bronchial asthma.
- Severe respiratory depression with hypoxia.
- 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.

4.4 Special warnings and precautions for use
DHC CONTINUS® tablets should be administered with caution in the elderly or patients with
- History of opiate abuse or dependence
- Raised intracranial pressure or head injury
- Biliary tract disorders
- Pancreatitis
- Impairment of hepatic function
- Severe renal dysfunction
- Chronic obstructive lung disease
- Cor pulmonale
- Bronchial asthma
- Respiratory depression with hypoxia
- Constipation
- Hypothyroidism
- Prostatic hypertrophy

DHC CONTINUS® tablets should be administered with caution in patients taking:
- Monoamine oxidase inhibitors (see section 4.5)
- CNS depressants (see section 4.5)

Respiratory depression and sedation
The major risk of opioid excess is respiratory depression.
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DHC CONTINUS® with benzoazepines or other CNS depressants (e.g., non-benzoazepine sedatives/hypnotics, anxiolytics, tranquilizers, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzoazepines 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).
If the decision is made to prescribe a benzoazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzoazepine 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 
deressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical 
response. Follow patients closely for signs and symptoms of respiratory depression and sedation. 
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).

**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® 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.

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.

**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).

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

**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 dihydrocodeine 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:
Dihydrocodeine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including other opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquillisers, gabapentin and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
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.

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

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 dihydrocodeine tartrate during pregnancy can result in neonatal opioid withdrawal syndrome.

Fertility
Prolonged treatment with DHC CONTINUS® tablets may potentially affect the reproductive function including menstrual disturbances, decreased libido and infertility.

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 \([ \geq 1\% ]\) 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: asthenia, fatigue, malaise, withdrawal syndrome
Not Known: drug withdrawal syndrome neonatal

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

Dihydrodorcodeine 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 <and special equipment for use, administration or implantation>
60 tablets. Bottles with polypropylene lid and polyethylene body.

6.6 Special precautions for disposal <and other handling>
None.
7 MEDICINE SCHEDULE
Controlled Drug C2.

8 SPONSOR
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10 DATE OF REVISION OF THE TEXT
July 2017

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