SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dihydrocodeine 120 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dihydrocodeine tartrate 120 mg.

Excipient with known effect:
Lactose anhydrous 54 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

White capsule-shaped tablet marked DHC 120.

4.1 Therapeutic indications

For the relief of severe pain in cancer and other chronic conditions.

Dihydrocodeine 120mg tablets are indicated for use in adults and children over 12 years of age.

4.2 Posology and method of administration

Posology

Adults and children over 12 years: The usual dose is one tablet 12-hourly.

Elderly: Dosage should be reduced.

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with dihydrocodeine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Paediatric population

Children 12 years or under: Not recommended.

Method of administration

Oral.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1; severe respiratory depression with hypoxia; severe chronic obstructive lung disease; severe cor pulmonale; severe bronchial asthma; paralytic ileus; acute alcoholism. As dihydrocodeine may cause the release of histamine, it should not be given during an asthma attack.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Dihydrocodeine should be administered with caution to the elderly or patients with:

- a history of opioid abuse or dependence
- raised intracranial pressure, intracranial lesions or head injury
- reduced level of consciousness of uncertain origin
- biliary tract disorders
- prostatic hypertrophy
- pancreatitis
- impairment of hepatic function
- severe renal dysfunction
- constipation
- an obstructive bowel disorder
- respiratory depression with hypoxia
- chronic obstructive pulmonary disease
- cor pulmonale
- bronchial asthma
- hypothyroidism
- sleep apnoea

The primary 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 pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Dihydrocodeine should be used with caution in patients taking monoamine oxidase inhibitors or within two weeks of such therapy.

Concomitant use of dihydrocodeine and sedative medicines such as benzodiazepines or related drugs 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 dihydrocodeine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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).

Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse and misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with dihydrocodeine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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

Dihydrocodeine tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of dihydrocodeine and may result in overdose effects (see section 4.9).

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 decrease in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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 and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines and alcohol.

Dihydrocodeine should be used with caution in patients taking monoamine oxidase inhibitors or within two weeks of such therapy.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dihydrocodeine in pregnant women. Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. Dihydrocodeine should only be used during pregnancy and labour if considered essential due to the risk of neonatal respiratory depression. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Breastfeeding

Administration to nursing women is not recommended as dihydrocodeine may be secreted in breast milk and may cause respiratory depression in the infant. It is advisable that dihydrocodeine only be administered to breast-feeding mothers if considered essential.

4.7 Effects on ability to drive and use machines

- Dihydrocodeine may cause drowsiness and, if affected, patients should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:

- The medicine has been prescribed to treat a medical or dental problem; and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.

- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

- Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

The adverse experiences listed below are classified by body system according to their incidence (common or uncommon). Common adverse drug experiences have an incidence of ≥ 1% and uncommon adverse drug experiences have an incidence of < 1%.

Undesirable Effects	Common (≥ 1%)	Uncommon (< 1%)	Not known (frequency cannot be estimated from the available data)
Immune system disorders		Angioedema	
Psychiatric disorders		Confusional state Hallucination Mood altered Dysphoria	Drug dependence (see section 4.4)
Nervous system disorders	Somnolence	Convulsions Dizziness Headache Paraesthesia Sedation	Sleep apnoea syndrome
Eye disorders		Blurred vision	
Ear and labyrinth disorders		Vertigo	
Vascular disorders		Hypotension Flushing	
Respiratory,		Dyspnoea	

thoracic and mediastinal disorders		Respiratory depression	
Gastrointestinal disorders	Abdominal pain Constipation Dry mouth Nausea Vomiting	Diarrhoea Paralytic ileus	
Hepato-biliary disorders		Biliary colic Hepatic enzymes increased	
Skin and subcutaneous tissue disorders		Hyperhidrosis Pruritus Rash Urticaria	
Renal and urinary disorders		Urinary retention Uretic spasm	
Reproductive system and breast disorders		Decreased libido	
General disorders and administration site conditions		Asthenia Fatigue Malaise Drug withdrawal syndrome Drug tolerance	Drug withdrawal syndrome neonatal

Prolonged use of a painkiller for headaches can make them worse.

Paediatric population
Neonatal respiratory depression and withdrawal symptoms may occur in the newborn of mothers undergoing treatment with dihydrocodeine (see section 4.6).

Reporting of adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response, or by an infusion. An infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on dihydrocodeine. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Additional/other considerations:

- Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations but there is no evidence to support this.

Dihydrocodeine tablets will continue to release and add to the dihydrocodeine load for up to 12 hours after administration and the management of overdosage should be modified accordingly. Gastric contents may therefore need to be emptied, as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02A A08

Dihydrocodeine is a semisynthetic narcotic analgesic with a potency between morphine and codeine. It acts on opioid receptors in the brain to reduce the patient's perception of pain and improve the psychological reaction to pain by reducing the associated anxiety.

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 Dihydrocodeine tablets and plasma levels are maintained throughout the twelve hour dosing interval.

Like other phenanthrene derivatives, dihydrocodeine is mainly metabolised in the liver with the resultant metabolites being excreted mainly in the urine. Metabolism of dihydrocodeine includes o-demethylation, n-demethylation and 6-keto reduction.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (anhydrous)

Hydroxyethylcellulose

Cetostearyl Alcohol

Magnesium Stearate

Purified Talc

Purified Water

6.2 Incompatibilities

None known

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

1. 20µm hard tempered aluminium foil backed PVdC/PVC blister packs (8 or 56 tablets).
2. Polypropylene containers with polyethylene lids (8, 56 or 250 tablets).
3. Polyethylene containers with polypropylene lids (56 tablets).

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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