SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dihydrocodeine 30mg Tablets BP.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dihydrocodeine tartrate 30 mg
Also contains Lactose monohydrate 155 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White, flat, circular, bevel edged plain tablet with breakline.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dihydrocodeine 30mg Tablets BP (as an analgesic) are indicated for the relief of moderate to severe pain. Dihydrocodeine 30mg Tablets BP are indicated in all painful conditions where an alert patient is desired, e.g. sciatica, osteo-arthritis, chronic rheumatoid arthritis, arthritis of the spine, peripheral vascular disease, post-herpetic neuralgia, Paget's disease, malignant disease, post-operative pain.

Because Dihydrocodeine, in the recommended doses, causes little or no respiratory depression, its use in the treatment of post-operative pain may reduce the risk of chest complications.

4.2 Posology and method of administration

Posology:

The analgesic effect is not materially enhanced by increasing the dose above that recommended below; in severe cases the interval between doses should be reduced to obtain the requisite analgesic cover.

Adults and children over 12 years: One tablet (30 mg) every 4 – 6 hours or at the discretion of the practitioner. Maximum dose in 24 hours 180mg (6 tablets)

Paediatric population: A more suitable dosage form is recommended for children under 12 years (e.g. elixir)

Elderly: Dosage should be reduced in the elderly

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).

Method of administration:
For oral use.
It is recommended that this product should be taken during or after food.

4.3 Contraindications

- Hypersensitivity to dihydrocodeine or other opioid analgesics or to any of the excipients listed in section 6.1.
- Respiratory depression
- Obstructive airways disease
- Acute alcoholism.
- Risk of paralytic ileus.
- Head injuries or conditions in which intracranial pressure is raised
- As dihydrocodeine may cause the release of histamine, it should not be given during an asthma attack.

4.4 Special warnings and precautions for use

Dihydrocodeine should be given in reduced doses or with caution to patients with asthma and decreased respiratory reserve. Avoid use during an acute asthma attack.

Dihydrocodeine should be avoided, or the dose reduced in patients with hepatic or renal impairment.

Dihydrocodeine should be given in reduced doses or with caution to; elderly patients, debiltated patients, adrenocortical insufficiency, prostatic hyperplasia, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, hypothyroidism or convulsive disorders, reduced level of consciousness of uncertain origin, biliary tract disorders, pancreatitis, constipation, cor pulmonale.

However, these conditions should not necessarily be a deterrent to use in palliative care.

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.

Use with caution in patients with a history of drug abuse

Alcohol should be avoided while under treatment with these tablets.

The risk and benefit of continued use should be assessed regularly by the doctor.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
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.

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).

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.

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 or 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.

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

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.

Important information regarding the ingredients in this medicine

Sodium: This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially (sodium-free).

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

The leaflet will state in a prominent position in the 'before taking' section:
- Do not take for longer than directed by your doctor.
- Taking dihydrocodeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.
- Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack-not boxed):

- Do not take for longer than directed by your doctor as taking dihydrocodeine regularly for a long time can lead to addiction

4.5 Interaction with other medicinal products and other forms of interaction

Dihydrocodeine may cause the release of histamine; hence this product should not be administered during an asthmatic attack and should be administered with caution in patients with allergic disorders.

The depressant effects of opioid analgesics (Dihydrocodeine) are enhanced by other central nervous system (CNS) depressants such as;

- Alcohol-enhanced hypotensive, sedative effect and respiratory depression
- Anaesthetics-may increase anaesthetic and sedative effect
- Sedating antihistamines-may enhance the CNS depressive effects when taken with opioids
- Anxiolytics or Hypnotics-may enhance CNS depressive effects when taken with opioids
- Tricyclic antidepressants-may enhance CNS depressive effects when taken with opioids
- Antipsychotics-enhanced hypotensive, sedative effect
- MAOIs taken with pethidine have been associated with severe CNS excitation or depression. Although this has not been documented with dihydrocodeine, it is possible that a similar interaction may occur with other opioid analgesics. Therefore, the use of dihydrocodeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Concomitant use of dihydrocodeine and ritonavir should be avoided due to the risk of toxicity.

Motility stimulants- Dihydrocodeine may antagonise the gastrointestinal effects metoclopramide and domperidone.

Cyclizine may counteract the haemodynamic benefits of opioids.

Mexiletine- Dihydrocodeine may delay absorption of mexiletine.

Cimetidine- may inhibit the metabolism of opioids

Sedative medicines such as benzodiazepines or related drugs: 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).

4.6 Fertility, Pregnancy and Breast-feeding

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

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.

Breast-feeding

Administration to nursing women is not recommended as dihydrocodeine may be secreted in breast milk and may cause respiratory depression in the infant.

4.7 Effects on ability to drive and use machines

Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

Effects such as paraesthesia, dizziness, vertigo, muscle rigidity, visual disturbances, drowsiness, confusion, syncope and hallucinations may occur. Do not drive or operate machinery if affected.

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 under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - 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 and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

The adverse drug reactions listed below are classified by system organ class according to their frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥

1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency		
	Common	**Uncommon**	**Not Known**
Immune system disorders		Angioedema	
Psychiatric disorders		Confusional state, hallucinations, mood altered, dysphoria	Euphoria, Drug dependence (see section 4.4)
Nervous system disorders	Somnolence	Convulsions, dizziness, headache, paraesthesia, sedation	Sleep apnoea Syndrome
Eye disorders		Blurred vision	Miosis
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			Bradycardia, tachycardia, palpitations
Vascular disorders		Hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, respiratory depression	
Gastrointestinal disorders	Abdominal pain, constipation, dry mouth, nausea, vomiting,	Diarrhoea, Paralytic ileus	
Hepatobiliary disorders		Biliary colic, hepatic enzymes increased	
Skin and subcutaneous tissue disorders		Hyperhidrosis, pruritus, rash, urticaria	
Renal and urinary disorders		Urinary retention, ureteric spasm	
Reproductive system and breast		Decreased libido	

disorders			
General disorders and administration site conditions		Asthenia, fatigue, malaise, Drug withdrawal syndrome, drug tolerance	Drug withdrawal syndrome neonatal

- Regular prolonged use of dihydrocodeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.
- 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 Suspected 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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms
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.

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

In the case of massive overdosage, administer naloxone hydrochloride intravenously (0.4 mg 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, 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.

*Ce*ntral *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

Absorption
Dihydrocodeine is well absorbed after oral administration. Peak plasma levels occur 1.6 - 1.8 hours after ingestion.

Plasma half-life has been reported to be 34 hours after oral ingestion. Dihydrocodeine is metabolised in the liver by 0- and N- demethylation.

Biotransformation
After oral administration the bioavailability of the drug is approximately 20%, indicating that the pre-systemic metabolism plays a substantial role in reducing the bioavailability of dihydrocodeine.

Elimination
Dihydrocodeine is excreted in the urine as unchanged drug and metabolites. The mean elimination half life ranges between 3.5 – 5 hours.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Lactose Monohydrate
Povidone
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Colloidal Anhydrous Silica

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Container: Do not store above 25° C. Keep the container tightly closed. Store in the original container.
Blister packs: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

HDPE tablet container with LDPP cap of 25, 50, 100, 250, 500, 1000 tablets.

AL/PVC blisters
Pack size: 14, 28, 30, 56, 60, 84 and 100 tablets

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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