SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Tablets BP 60 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate BP 60 mg per tablet. Each tablet contains 36.00 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3.0 Pharmaceutical Form

Codeine Phosphate BP 60 mg tablet.

Codeine Phosphate Tablets 60mg are white normal convex tablets engraved with RGM on one side with A025 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine Phosphate Tablets BP is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone)
Dry or painful cough

Diarrhoea

4.2 Posology and method of administration

Treatment goals and discontinuation
Before initiating treatment with Codeine Phosphate Tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4). Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine in order

to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

For Mild to Moderate Pain

Adults:

Codeine should be used at the lowest effective dose for the shortest period of time. The dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240mg.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Elderly:

Dosage should be reduced in elderly patients.

Paediatric Population:

Children aged 12 years to 18 years:

The recommended codeine dose for children 12 years and older should be 30-60mg every 6 hours when necessary up to a maximum dose of codeine of 240mg daily. The dose is based on the body weight (0.5-1mg/kg).

Children aged less than 12 years:

Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

For dry or painful cough

Adults:

15-30mg 3-4 times daily.

Elderly:

Dosage should be reduced in elderly patients

Paediatric Population:

Children aged less than 12 years:

Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough see section 4.3.

Children aged 12 years to 18 years

Codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough (see section 4.4).

Diarrhoea

Adults:

30mg three to four times daily (range 15-60mg)

Elderly:

Dosage should be reduced in elderly patients

Paediatric Population:

Not recommended.

Codeine Phosphate Tablets should not be used longer than necessary.

Method of administration

Oral route

4.3 Contraindications

Acute respiratory depression, hypersensitivity to codeine or other opioid analgesics or to any of the excipients listed in section 6.1, obstructive airways disease, liver disease, severe hepatic dysfunction, acute alcoholism.

Use should be avoided in patients with raised intracranial pressure or head injury (in addition to the risk of respiratory depression and increased intracranial pressure, may affect pupillary and other responses vital for neurological assessment).

Codeine should not be given to comatose patients.

Codeine is also contraindicated in conditions where inhibition of peristalsis is to be avoided, where there is a risk of paralytic ileus, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis) or diarrhoea caused by poisoning.

Codeine is also contraindicated in the following:

- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)

- In women during breastfeeding (see section 4.6).

- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

Use with caution or in reduced doses in asthma and decreased respiratory reserve; avoid use during an acute asthma attack (see 4.3 Contraindications). It should only be used with caution in reduced dose in elderly patients or debilitated patients, or in patients with hypotension, hypothyroidism, prostatic hypertrophy, adrenocortical insufficiency, inflammatory or obstructive bowel disorders, urethral stricture, shock, convulsive disorders, myasthenia gravis. It should be avoided or the dose reduced in patients with renal or hepatic impairment (see 4.3 Contraindications, liver disease). Use with caution in those with a history of drug abuse.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	**Prevalence %**
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% -2%

Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Opioid analgesics should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. If the use of codeine is considered essential then great care should be taken in patients taking MAOIs or within 14 days of stopping MAOIs (see section 4.5).

The risk-benefit of continued use should be assessed regularly by the prescriber.

<u>Drug dependence, tolerance and potential for abuse</u>

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Codeine Phosphate Tablets. Repeated use of Codeine Phosphate Tablets can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Codeine Phosphate Tablets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Codeine Phosphate Tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

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.

Discontinuation should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms.

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 Codeine Phosphate.

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.

Sleep-related breathing disorders

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. In patients who present with CSA, consider decreasing the total opioid dosage.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Hepatobiliary disorders
Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Lactose
Codeine Phosphate Tablets contain lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
30 & 60mg tablets: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is
to say essentially ‘sodium-free’.
The 15mg tablets do not contain sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: the hypotensive, sedative and respiratory depressive effects of alcohol may be enhanced.

Anaesthetics: concomitant administration of codeine and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.

Anti-arrhythmics: codeine delays the absorption of mexiletine. The analgesic activity of codeine is likely to be significantly impaired by quinidine which impairs codeine metabolism.

Antidepressants: The depressant effects of opioid analgesics may be enhanced by tricyclic antidepressants.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Antihistamines: concomitant administration of codeine and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

The concomitant use of codeine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Antipsychotics: enhanced sedative and hypotensive effect.

Anxiolytics and hypnotics: enhanced sedative effect.

Domperidone and metoclopramide: codeine antagonises the effect of cisapride, metoclopramide and domperidone on gastrointestinal activity.

Anticholinergics (e.g. atropine) – risk of severe constipation which may lead to paralytic ileus and/or urinary retention if Codeine phosphate and atropine taken concomitantly.

Sodium oxybate: concomitant administration of codeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Ritonavir may increase plasma levels of opioid analgesics such as codeine.

Ulcer-healing drugs: Cimetidine may inhibit the metabolism of codeine resulting in increased plasma concentrations.

Interference with laboratory tests: Opioids may interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy:

As with all medications caution should be exercised during pregnancy, especially in the first trimester. A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine.

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.

Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.

Breast-feeding
Codeine is contraindicated in women during breastfeeding (see section 4.3).

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

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

Codeine produces sedation and may also cause changes in vision, including blurred or double vision therefore treatment may impair ability to drive and use machines. If affected, patients should not drive or operate machinery.

The effects of alcohol are enhanced by opioid analgesics.

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

Regular prolonged use of codeine 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.

Tolerance and some of the most common side effects – drowsiness, nausea, and vomiting, and confusion – generally develops with long term use.

Immune system disorders: maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate; fever, splenomegaly and lymphadenopathy also occurred.

Endocrine disorders: hyperglycaemia.

Metabolism and nutrition disorders: anorexia.

Psychiatric disorders:
mental depression, hallucinations and nightmares, restlessness, confusion, mood changes, euphoria and dysphoria.
Frequency unknown: drug dependence (see section 4.4).

Nervous system disorders: convulsions (especially in infants and children), dizziness, drowsiness, headache (prolonged use of a painkiller for headaches can make them worse). Raised intracranial pressure may occur in some patients.

Eye disorders: blurred or double vision or other changes in vision. Miosis.

Ear and labyrinth disorders: vertigo.

Cardiac disorders: tachycardia, palpitations and bradycardia.

Vascular disorders: postural hypotension, facial flushing. Large doses produce hypotension.

Respiratory, thoracic and mediastinal disorders: Dyspnoea. Large doses produce respiratory depression.

Gastrointestinal disorders: nausea, vomiting, constipation, dry mouth, stomach cramps
not known: pancreatitis.

Hepatobiliary disorders: Biliary spasm (may be associated with altered liver enzyme values).
not known: sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders: allergic reactions such as skin rashes, urticaria, pruritus, sweating and facial oedema.

Musculoskeletal, and connective tissue disorders: Uncontrolled muscle movements. Muscle rigidity may occur after high doses.

Renal and urinary disorders: difficulty with micturation, urinary retention, ureteric spasm, dysuria. An antidiuretic effect may also occur with codeine.

Reproductive system and breast disorders: sexual dysfunction, erectile dysfunction, decreased potency. Decreased libido.

General disorders and administration site conditions: malaise, tiredness, hypothermia.
Uncommon: drug withdrawal syndrome.

Drug dependence

Repeated use of Codeine Phosphate Tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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.

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

Symptoms: 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 triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid over dosage. Nausea and vomiting are common. Other opioid overdose symptoms include hypothermia, confusion, convulsions, severe dizziness, severe drowsiness, hypotension and tachycardia (possible but unlikely), nervousness or restlessness, excitement, hallucinations, bradycardia, circulatory failure, slow or troubled breathing, severe weakness, convulsions, especially in infants and children. Rhabdomyolysis, progressing to renal failure, has been reported in over dosage with opioids.

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 acute overdosage with respiratory depression or coma, the specific opioid antagonist naloxone is indicated using one of the recommended dose regimens– repeated doses may be required in a seriously poisoned patient as naloxone is a competitive antagonist with a short half life. Patients should be observed closely for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opium alkaloids and derivatives. ATC code R05D A04.

Codeine has similar uses to morphine but is much less potent as an analgesic and has only mild sedative effects.
Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as Paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Codeine is well absorbed from the gastrointestinal tract following oral administration.

It is metabolised in the liver to morphine and norcodeine which are both excreted in the urine partly as conjugates with glucuronic acid. Most of the excretion products appear in the urine within 6 hours and up to 86% of the dose is excreted in 24 hours. About 70% of the dose is excreted as free codeine, 10% as free and conjugated morphine and a further 10% as free or conjugated norcodeine. Only traces are found in the faeces. The plasma half life is between approximately 3 and 4 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber, which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose
Talc
Magnesium stearate
Sodium laurilsulfate (not present in the 15 mg tablet)

6.2. Incompatibilities

None reported.

6.3 Shelf life

3 years for opaque plastic containers and amber glass bottles.
3 years for blister packs

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Codeine phosphate tablets are packed in the following pack types and pack sizes.

Opaque plastic containers (securitainers) fitted with plastic caps for all pack sizes.

Amber glass bottles for all pack sizes.

Opaque plastic container composed of either high density polypropylene or high density polyethylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene for all pack sizes (28, 30, 42, 50, 56, 84, 100, 112, 250, 500, 1000 and bulk) with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler.

Blister packs of aluminium opaque/PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 42, 56, 84 and 112.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill,
Basingstoke, RG21 8SR,
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8. MARKETING AUTHORISATION NUMBER

PL 20416/0057

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2009

10 DATE OF REVISION OF THE TEXT

02/04/2026