SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Tablets BP 15 mg
Codeine Phosphate Tablets BP 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15mg Codeine Phosphate Ph Eur.
Excipient with known effect: Also contains 34.50 mg of lactose

Each tablet contains 30mg Codeine Phosphate Ph Eur.
Excipient with known effect: Also contains 29.40 mg of lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets
A smooth, round, flat faced, bevelled edge plain white to off white tablet.

Tablets
A smooth, round, flat faced, bevelled edge plain white to off white tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

1. Indicated as an analgesic for the relief of mild to moderate pain.
   Codeine is indicated in children 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).
2. For the symptomatic relief of unproductive cough and diarrhoea.

4.2. Posology and method of administration

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

Posology

For Mild to Moderate Pain

Adults:

Long term use - the risk benefit should be assessed regularly by the prescriber.

Codeine should be used at the lowest effective dose for the shortest period of time. This 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 240 mg.

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.

Analgesia

Adults: 30 – 60 mg every four hours to a maximum dosage of 240mg daily.

The analgesic effect is not materially enhanced by increasing the dose to a greater level than that recommended above.

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

Paediatric population
Children aged 12 years to 18 years:
The recommended codeine dose for children 12 years and older should take 30 to 60mg every 6 hours when necessary up to a maximum dosage of 240 mg daily. The dose is based on the body weight (0.5-1mg/kg).

Children aged less than12 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)

Diarrhoea

Adults and children over 12 years: 15-60 mg three to four times daily

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

Children under 12 years: Not recommended.

Cough
Adults and children over 12 years: 15-30 mg three to four times daily

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

Paediatric population:

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).

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).

Method of Administration

For oral use.

4.3. Contraindications

- Hypersensitivity to codeine, other opioid analgesics or any of the excipients listed in section 6.1
- Acute respiratory depression
- Obstructive airways disease, e.g., emphysema
- Asthma- opioids should not be administered during an asthma attack
- Hepatic failure
- Head injuries or conditions where intracranial pressure is raised (in addition to the risk of respiratory depression and increased intracranial pressure, may affect pupillary and other responses vital for neurological assessment).
- Acute alcoholism
- Risk of paralytic ileus
- Liver disease, severe hepatic dysfunction.
- 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 children below the age of 12 years for the symptomatic treatment of cough due to increased risk of developing serious and life-threatening adverse reactions
- 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

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.

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.

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.

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

Concomitant use of codeine phosphate 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 codeine phosphate 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).

Codeine phosphate should be used with caution in the following conditions:

- There is a possible risk of CNS excitation or depression with concomitant use of opioids with MAOIs and use is not recommended (see section 4.5)
- Hepatic impairment - avoid if severe. Codeine may precipitate coma
- Renal impairment (see 4.3 Contraindications, liver disease).
- Hypothyroidism
- Inflammatory or obstructive bowel disease - codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure, therefore should be used with caution in diverticulitis, acute colitis, diarrhoea associated with pseudomembranous colitis or after bowel surgery
- Convulsions - may be induced or exacerbated
- Drug abuse or dependence (including alcoholism)
- Gall bladder disease or gall stones - opioids may cause biliary contraction. Avoid in biliary disorders
- Gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility
- Urinary tract surgery – following recent surgery patients will be more prone to urinary retention caused directly by spasm of the urethral sphincter, and via constipation caused by codeine
- Phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine
- Prostatic hypertrophy
- Adrenocortical insufficiency, e.g., Addison's Disease
- Hypotension and shock
- Myasthenia gravis
- Reduced respiratory function or history of asthma; asthma attack (see 4.3 Contraindications).
- Pregnancy and breast feeding (see section 4.6)
- Elderly patients may metabolise and eliminate opioid analgesics more slowly than younger patients (see section 4.2).
- convulsive disorders
- elderly patients or debilitated patients.

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, nausea, vomiting, shallow breathing, small pupils, constipation, lack of appetite and somnolence. 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 thengreat 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.

The leaflet text will state in a prominent position section 2 “What you need to know before you take Codeine Phosphate tablets”.

- Do not take for longer than directed by your prescriber.
- Taking codeine 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 regularly for headaches too often or for too long can make them worse.

The label will state:
Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

Important information regarding the ingredients in this medicine

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant Combinations not recommended (see section 4.4):

- MAOIs (linezolid, moclobemide and selegiline) due to the possible risk of excitation or depression – avoid concomitant use and for 2 weeks after discontinuation of MAOI

Combinations to be used with caution:

Respiratory related

- Sedative medicines such as benzodiazepines or related drugs (chlorpromazine, diazepam, temazepam) - 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).
- Alcohol - enhanced sedative and hypotensive effect, increased risk of respiratory depression of alcohol may be enhanced.
- Sedative antihistamines - enhanced sedative and hypotensive effect and increased risk of respiratory depression
- Hypnotics and anxiolytics - enhanced sedative effect, increased risk of respiratory depression
- Sodium oxybate: concomitant administration of codeine and sodium oxybate may cause increased CNS depressionand/or respiratory depression and/or hypotension

Gastrointestinal related

- Anticholinergics (eg atropine) - risk of severe constipation which may lead to paralytic ileus, and /or urinary retention
- Metoclopramide and domperidone – codeine antagonises the effect of cisapride, metoclopramide and domperidone on GI activity

- Antidiarrhoeal drugs (eg loperamide, kaolin) – increased risk of severe constipation.

CNS related
- Anaesthetics: concomitant administration of codeine and anaesthetics may cause increased CNS depression and/or respiratory depression and/or hypotension.
- Tricyclic antidepressants - enhanced sedative effect
- Antipsychotics - enhanced sedative and hypotensive effect
- Opioid antagonists e.g., buprenorphine, naltrexone, naloxone – may precipitate withdrawal symptoms
- Quinidine- reduced analgesic effect
- Antihypertensive drugs - enhanced hypotensive effect.

Pharmacokinetic interactions
- Ciprofloxacin - avoid premedication with opioids as they reduce plasma ciprofloxacin concentrations
- Ritonavir may increase plasma levels of opioid analgesics such as codeine
- Anti-arrhythmics: codeine delays the absorption of mexiletine. The analgesic activity of codeine is likely to be significantlyimpaired by quinidine which impairs codeine metabolism.
- Ulcer-healing drugs: Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

Interference with laboratory tests: Opioids may interfere with gastric emptying studies as they delay gastric emptying andwith hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincterof 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.
During labour opioids enter the foetal circulation and may cause respiratory depression in the neonate. Respiratory malformation in neonates may be associated with exposure to codeine during pregnancy. Gastric stasis and a risk of inhalation

pneumonia could occur in the mother during labour. Administration should be avoided during the late stages of labour and during the delivery of a premature infant.

Breast-feeding
Codeine is contraindicated in women during breast-feeding (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. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Opioid toxicity
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. Effect on ability to drive and use machines

Codeine 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 confusion, drowsiness, dizziness, hallucinations, sedation, blurred or double vision or convulsions may occur. The effects of alcohol are enhanced with this combination. 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

- **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.

Nervous system disorders:drowsiness, dizziness, changes in mood, , CNS excitation (restlessness/ excitement), convulsions (especially in infants and children), headache (prolonged use of a painkiller for headaches can make them worse), , raised intracranial pressure, tolerance

- **Psychiatric disorders:** mental depression, hallucinations and nightmares, restlessness, confusion, mood changes, euphoria and dysphoria.

Frequency unknown: Drug dependence (see section 4.4)

- **Eye disorders:** miosis, blurred or double vision or other changes in vision.

- **Cardiac disorders:** bradycardia, palpitations, , tachycardia.

- **Respiratory, thoracic and mediastinal disorders:** respiratory depression with larger doses, Dyspnoea.

- **Gastrointestinal disorders:** constipation (too constipating for long-term use), nausea, vomiting, dry mouth, stomach cramps, pancreatitis.

- **Musculoskeletal, connective tissue and bone density:** Uncontrolled muscle movements, muscle rigidity may occur after high doses.

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

- **Reproductive system and breast disorders:** decrease in libido and potency, sexual dysfunction, erectile dysfunction.

- **Endocrine disorders:** hyperglycaemia.

- **Metabolism and nutrition disorders**: anorexia.

- **Ear and labyrinth disorders**: vertigo.

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

Hepatobiliary disorders: Biliary spasm (may be associated with altered liver enzyme values).

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

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

- **Withdrawal effects:**

Uncommon; abrupt withdrawal precipitates drug withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration, and increase in heart rate, respiratory rate and blood pressure. NOTE - tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

- 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.

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 professional 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

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, pupils may be pin point in size and respiratory depression is considered indicative of opioid over dosage with dilation of the pupils occurring as hypoxia develops. Nausea and vomiting are common. Other opioid overdose symptoms include hypothermia, confusion, convulsions, severe dizziness, severe drowsiness, hypotension and tachycardia are possible but unlikely, nervousness orrestlessness, 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 overdosage 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 the 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 poisonedpatient 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: ATC Code - R05D A04

Codeine is an analgesic with uses similar to those of morphine but it is much less potent as an analgesic and has only mild sedative effects. It is also used in the treatment of cough and diarrhoea.

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

Absorption and Distribution
Codeine and its salts are well absorbed from the gastrointestinal tract following oral administration and ingestion of codeine phosphate produces peak plasma concentrations in about one hour. Plasma half-life is between 3 to 4 hours and oral/intramuscular analgesic ration is approximately 1:1.5

Biotransformation
It is metabolised by O-and N-Demethylation in the liver to morphine and norcodeine which are both excreted in the urine partly as conjugates with glucuronic acid.

Elimination
Codeine and its metabolites are excreted almost entirely by the kidney, mainly 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.

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

Lactose
Stearic acid

6.2 Incompatibilities

None known

6.3. Shelf life

For PL 17907/0168:
3 years

For PL 17907/0169:
4 years for blister packaging
3 years for HDPE container

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 LDPE caps
Pack size: 25, 50, 100, 250, 500 and 1000 tablets.

Blisters comprising of 250micron PVC film and 20micron aluminium foil packed in cartons.
Pack size: 14, 28, 30, 56, 60 and 84 tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd
Unit 3, Canalside
Northbridge Road
Berkhamsted, Herts
HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0168
PL 17907/0169

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 16 February 2005
Renewal of the Authorisation: 12 March 2009

10 DATE OF REVISION OF THE TEXT

12/07/2023