SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Tablets BP 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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). For the symptomatic relief of unproductive cough and diarrhoea

4.2. Posology and method of administration

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

Analgesia
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.

Paediatric population

Children aged 12 years to 18 years :

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

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

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).

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

Method of Administration
For oral use.

4.3. Contraindications

- Hypersensitivity to codeine, other opioids 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
- 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)
- Acute alcoholism
- 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
- 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.

4.4. Special warnings and precautions for use

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

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- 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
- Hypothyroidism
- Inflammatory 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
- 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).
- The risk benefit of continued use should be assessed regularly by the prescriber

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 they will not obtain adequate analgesic effects. 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 prescribeddoses. 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%

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated (see section 4.3):

• MAOIs (and drugs with MAOI action such as 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
• Alcohol - enhanced sedative and hypotensive effect, increased risk of respiratory depression
• Sedative antihistamines - enhanced sedative and hypotensive effect and increased risk of respiratory depression

- Hypnotics and anxiolytics - enhanced sedative effect, increased risk of respiratory depression

Gastrointestinal related

- Anticholinergics (eg atropine) - risk of severe constipation which may lead to paralytic ileus, and /or urinary retention
- Metoclopramide and domperidone – antagonise effect on GI activity
- Antidiarrhoeal drugs (eg loperamide, kaolin) – increased risk of severe constipation.

CNS related

- Anaesthetics - enhanced sedative and hypotensive effect
- 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.
- Sodium oxybate- concomitant administration of codeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Pharmacokinetic interactions

- Ciprofloxacin when used as surgical prophylaxis, - avoid premedication with opioids as they reduce plasma ciprofloxacin concentrations
- Ritonavir may increase plasma levels of opioid analgesics such as codeine
- Mexiletine - delayed absorption of mexiletine
- 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 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

Risk benefit must be considered because opioid analgesics cross the placenta. Studies in animals have shown opioids to cause delayed ossification in mice and increased resorption in rats.

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 physical dependence in the fetus, leading to withdrawal symptoms in the neonate. During labour opioids enter the fetal 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 breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed 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.

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, blurred or double vision or convulsions may occur. The effects of alcohol are enhanced with this combination. Patients should be advised, that if affected, they should not drive, operate machinery or take part in any activities where such impairment could put themselves or others at risk.

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:** (may be caused by histamine release) – including rash, urticaria, pruritus, difficulty breathing, increased sweating, redness or flushed face, oedema

- **Nervous system disorders:** confusion, drowsiness, malaise, tiredness, vertigo, dizziness, convulsions, headache, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia.

- **Psychiatric disorders:** mood changes, depression, hallucinations (seeing or hearing things that are not real), restlessness, excitation, nightmares, confusion.

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

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

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

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

- **Hepatobiliary disorders:** biliary spasm.

- **Musculoskeletal, connective tissue and bone density:** muscle rigidity.

- **Renal and urinary disorders:** ureteral spasm, antidiuretic effect, urinary retention.

- **Reproductive system and breast disorders:** decrease in libido and potency.

- **Withdrawal effects:** abrupt withdrawal precipitates a 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.

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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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 overdosage 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 (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 overdosage with opioids.

Management
Management 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 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

ATC Code- R05D A04

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. It is also used in the treatment of

cough and diarrhoea. 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 and its salts are readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by O-and N-Demethylation in the liver to morphine and nor codeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours

5.3 Preclinical safety data

There are no preclinical 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,
Stearic acid

6.2 Incompatibilities

None known

6.3. Shelf life

4 years for blister packaging
3 years for amber-glass bottle
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

A round amber-glass bottle with a tin-plate screw cap fitted with a waxed aluminium faced pulpboard liner.
Pack size: 100 or 500 tablets

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

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