SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate 30 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30mg Codeine Phosphate.

Excipient(s) with known effect
Each 30 mg tablet contains 27 mg lactose.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White to off white, biconvex tablets, marked 'APS' on one side and '30/0508' on the reverse; or marked 'APS' over '0508' on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Codeine Phosphate Tablets are indicated in patients older than 12 years of age for the treatment of mild to moderate acute pain which is not relieved by other analgesics such as paracetamol or ibuprofen (alone), diarrhoea and troublesome cough.

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

Posology
Codeine should be used at the lowest effective dose for the shortest period of time.

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.

Adults

Analgesic use

30-60 mg every four hours when necessary, up to a maximum of 240 mg daily.

Anti-diarrhoeal use

30 mg three to four times daily.

Antitussive use

15-30 mg three to four times daily.

Paediatric population

Children under 12 years

Not suitable.

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

Children aged 12 years to 18 years:

Analgesic use

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

Antitussive use

Codeine Phosphate 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).

1 to 2 mg/kg bodyweight daily in 4 to 6 divided doses.

The use of cough suppressants containing codeine is not generally recommended in children.

Anti-diarrhoeal use

Not recommended

Elderly

The adult dosage should be reduced.

Method of administration

For oral administration.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Codeine Phosphate is contraindicated in patients with hepatic disease, acute respiratory depression, acute alcoholism, acute ulcerative colitis, antibiotic-associated colitis and where there is a risk of paralytic ileus, in children below the age of 12 years for symptomatic treatment of cough due to an increased risk of developing serious and life-threatening adverse

reactions, in patients with raised intracranial pressure or with significant head injury (in addition to interfering with respiration, it affects papillary responses vital for neurological assessment), in women during breastfeeding (see section 4.6), 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 patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

4.4. Special Warnings and precautions for use

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

- Patient 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 central nervous system (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.

Codeine is a narcotic analgesic. Tolerance, psychological and physical dependence may occur, especially if large doses are used. Cough suppression may cause sputum retention, which can be harmful in patients with chronic bronchitis.

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.

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.

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.

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).

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% to 2%

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.

Paediatric population

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 ultrarapid 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.

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

The leaflet will state in a prominent position in the 'before taking' section:

- 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 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 prescriber as taking codeine regularly for a long time can lead to addiction.

Excipient(s)

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

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant combinations not recommended (see section 4.4):
- MAOIs (e.g. linezolid, moclobemide, selegiline) due to the possible risk of CNS 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 (e.g. 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 (*e.g.* 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.

Pharmacokinetic interactions
- Ciprofloxacin - avoid premedication with opioids as they reduce plasma ciprofloxacin concentration
- Ritonavir may increase plasma levels of opioid analgesics such as codeine
- Mexiletine and flecainide- delayed absorption of mexiletine and flecainide
- Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

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 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.

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.

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.

Although there is inadequate evidence of safety in human pregnancy, codeine and its active metabolite has been widely used for many years without apparent ill-consequence, and animal studies have not shown any hazard.

Breast-feeding

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.

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 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 sedation, confusion, drowsiness, dizziness, hallucinations, 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

List of adverse reactions

Psychiatric disorders
Mood changes, depression, hallucinations, dysphoria, drug dependence (see section 4.4)

Nervous system disorders
Headache, drowsiness, confusion, malaise, tiredness, dizziness, CNS excitation (restlessness/excitement), nightmares, raised intracranial pressure, hypothermia, convulsions.

Eye disorders
Miosis, blurred or double vision

Ear and labyrinth disorders
Vertigo

Cardiac disorders
Tachycardia, bradycardia, palpitations

Vascular disorders
Hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Respiratory depression with larger doses

Gastrointestinal disorders
Nausea, vomiting, constipation, dry mouth, pancreatitis

Hepatobiliary disorders
Biliary spasm

Skin and subcutaneous tissue disorders
Rash

Musculoskeletal and connective tissue disorders
Muscle rigidity

Renal and urinary disorders
Ureteral spasms, antidiuretic effect, urinary retention

Reproductive system and breast disorders
Decrease in libido and potency

General disorders and administration site conditions:
Drug withdrawal syndrome

NOTE – tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Faecal impaction may occur, particularly in the elderly. Such impaction can lead to incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction.

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 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 pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely. In case of overdose, death may occur.

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.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe 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: RO5D AO4

Mechanism of action

Codeine produces effects on the CNS and the bowel. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its conversion effect is due to its conversion into morphine.

Pharmacodynamic effects

Codeine, particularly with other analgesics such as paracetamol, has been shown effective in acute nociceptive pain. These effects include analgesia, drowsiness, mood changes, respiratory depression, decreased gastro-intestinal motility, nausea, vomiting and alterations of the endocrine and autonomic nervous systems.

A major limitation of its clinical use is the potential for development of tolerance and physical dependence in long term use.

5.2. Pharmacokinetic properties

Absorption

Codeine is readily absorbed from the gastro-intestinal tract.

Biotransformation

It is metabolised in the liver and excreted mainly in the urine. About 10% of a dose is demethylated to form morphine, which may account for its analgesic effect. Oral availability is approximately 66 %, the plasma half-life is 2.5 to 3 hours with a duration of action of 4 to 6 hours.

5.3. Preclinical safety data

Preclinical information has not been included because the safety profile of codeine phosphate has been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dextrin
Lactose Monohydrate
Magnesium Stearate (E572)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Do not store above 25°C. Protect from light.

6.5. Nature and content of container

Blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

HDPE or polypropylene containers with caps or child resistant closures in packs of 100, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/5061R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 18 February 1982
Date of last renewal: 26 March 2002

10. DATE OF (PARTIAL) REVISION OF THE TEXT

12/04/2022

POM