SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate 30mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate 30mg

For excipients see 6.1

3. PHARMACEUTICAL FORM

Oral – tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Codeine 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

Oral route

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

For Mild to Moderate Pain

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 be 30-60mg 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).

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).

Elderly:

Dosage should be reduced in elderly patients.

For dry or painful cough

Adults:

15-30mg, 3-4 times daily

Children:

Not recommended

Elderly:

Dosage should be reduced in elderly patients

Diarrhoea

Adults:

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

Children:

Not recommended

Elderly:

Dosage should be reduced in elderly patients

4.3 Contraindications

Acute respiratory depression, hypersensitivity to codeine or other opioid analgesics or to any of the excipients, 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 or 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. Discontinuation should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms.

<u>CYP2D6 metabolism</u>

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine as it contains lactose.

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.

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.

4.5 Interactions 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.

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.

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

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 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.

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.

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 to use machines

Codeine produces sedation and may also cause changes in vision, including blurred or double vision. 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 of 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, pancreatitis.

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.

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.

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 ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal.

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 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

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 350mg or a child more than 5mg/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

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 Pre-Clinical 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
Acacia spray-dried
Maize starch
Magnesium stearate
Stearic acid

6.2 Incompatibilities

None

6.3 Shelf Life

36 months for polypropylene/polyethylene containers

36 months for blister packaging

6.4 Special Precautions for Storage

Do not store above 25^0C

Store in the original container

6.5 Nature and Contents of Container

100, 250, 500, 1,000 and 10,000 tablets in polypropylene/polyethylene containers.

100 tablets in amber glass bottles with plastic cap.

28, 30, 56, 60, 84 and 90 tablets in polypropylene/polyethylene containers in cartons.

28, 30, 56, 60, 84, 90 and 100 tablets in blister pack strips of 20 micron, hard tempered aluminium foil, coated with PVC compatible heat seal lacquer on the reverse side, and PVC film, in cartons.

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd.
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

MA143/02101

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18th August 2006/23rd May 2016

10. DATE OF REVISION OF THE TEXT

February 2022