SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Linctus BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine Phosphate BP 15mg/5ml dose.

Excipients of known effect
Per 5ml dose, this medicine contains:
5.2mg Benzoic acid
81.7mg Propylene Glycol
133.75mg Invert Syrup
4g Sucrose
0.05mg Sunset Yellow Dye
0.2mg Quinoline Yellow

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Linctus.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in adults for relief of the symptoms of dry or irritating coughs.

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).

Oral.

Adults:
One 5ml spoonful.

Elderly:
Use with caution, a reduced dose can be recommended by a doctor.

Paediatric population:
Codeine should not be used for the treatment of children under the age of 18 years.

Dosage schedule:
The dose may be repeated after four hours if required, but not more than 4 doses in any 24 hours.

4.3 Contraindications

Suspected opiate abuse, known hypersensitivity to codeine or to any of the other ingredients.
In cases of liver failure, respiratory depression, or patients at risk of paralytic ileus.
In patients with raised intracranial pressure or head injury.
In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
During an acute asthmatic attack.
Children under 18 years of age.
In women during breastfeeding (see section 4.6)

Special warnings and precautions for use

Use with caution in patients with renal and hepatic impairment(but avoid if severe), patients suffering from asthma or other respiratory disorders, or patients with a history of asthma, hypotension, shock, myasthenia gravis, cardiac arrhythmias, acute abdomen, gallstones, prostatic hypertrophy, urethral stenosis, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders.

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).

Use with caution in the elderly, as codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and, rarely, colonic obstruction. Prolonged use could aggravate irritable bowel syndrome.

A reduced dose is recommended in elderly or debilitated patients, in hepatic and renal impairment (but avoid if severe), in hypothyroidism, and in adrenocortical insufficiency. Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this

is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence or in acute alcoholism.

Codeine Linctus and other cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

If symptoms persist consult your doctor.

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. General symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

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%

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Codeine Linctus contains Quinoline Yellow Solution Compound which contains Sunset Yellow (E110) and Quinoline Yellow (E104). Sunset Yellow may cause allergic reactions.

Precautions/warnings to be declared on labels:

Do not exceed the stated dose.
Keep out of the sight and reach of children.

This product contains 4g of sucrose per dose. To be taken into account in people with diabetes. It also contains invert syrup. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

It contains a small amount of ethanol (alcohol), less than 100mg per 5ml.

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 relief as initially experienced. Patients may also supplement their treatment with additional medicines. 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Antimuscarinics: codeine phosphate may increase the risk of antimuscarinic side effects such as dry mouth, urine retention and constipation (but this does not generally apply to antimuscarinics taken by inhalation).

Metabolism of codeine is accelerated by rifampicin leading to reduced effect.

As an opioid analgesic, codeine phosphate may potentiate the effects of tranquillisers such as barbiturates, general anaesthetics, anxiolytics and hypnotics, sedatives and alcohol.

Possible CNS excitation or depression (hypertension or hypotension) can occur when opioid analgesics are given with antidepressants such as moclobemide (a reversible MAO-A inhibitor). The sedative effects of codeine can possibly be increased when given with tricyclic antidepressants, with anxiolytics or hypnotics, or with sedating antihistamines. Antipsychotic medicines can enhance hypotensive and sedative effects when opioid analgesics are given with antipsychotics.

Monoamine oxidase inhibitors: 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, including MAO-B inhibitor selegiline. This may also apply to the antibacterial linezolid, which is a reversible, non-selective MOA inhibitor.

Anti-emetics: The reduction in intestinal motility caused by codeine may delay the absorption or antagonise the gastrointestinal effects of other drugs e.g. metoclopramide and domperidone.

Metabolism of opioid analgesics is inhibited by cimetidine leading to increased plasma concentration.

Anti-arrhythmics: May delay the gastro-intestinal absorption of mexiletine or quinidine (which may also reduce the efficacy of codeine).

Opioid analgesics enhance the effects of sodium oxybate, used to treat symptoms of narcolepsy, and concomitant use should be avoided.

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

The product should not be used during pregnancy unless considered necessary by the physician and should be avoided during the first trimester. Opioid

administration in the third trimester may cause respiratory depression in the newborn, withdrawal effects in neonates of dependent mothers, gastric stasis and risk of inhalation pneumonia in the mother during labour. 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.

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant. At normal therapeutic doses codeine and its active metabolite 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 ultrarapid metaboliser of codeine 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. The infant itself may be a CYP2D6 ultra-rapid metaboliser. In either case on very rare occasions this may result in symptoms of opioid toxicity in the infant. (See also section 4.4).

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

Using the dose recommended, Codeine Linctus is not considered to be a hazard, however the use of codeine phosphate at higher doses or in more sensitive individuals may cause sedation, dizziness and nausea. Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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

The following undesirable effects have been reported following use of codeine phosphate or opioid analgesics and may arise following use of Codeine Linctus. The frequency of adverse effects cannot be estimated from available data.

Psychiatric disorders: hallucinations, dysphoria, euphoria, mood changes, restlessness, confusion, drug dependence (see section 4.4).

Nervous system disorders: dizziness, drowsiness, seizures, addiction, tolerance, dependence, headache, vertigo, malaise, sleep disturbances.

Eye disorders: miosis, visual disturbances.

Cardiac disorders: palpitations, bradychardia, tachycardia.

Vascular disorders: postural hypotension, hypothermia, facial flushing, oedema.

Respiratory, thoracic and mediastinal disorders: respiratory depression.

Gastrointestinal disorders: nausea, vomiting, constipation, abdominal pain, anorexia, pancreatitis, dry mouth.

Hepatobiliary disorders: biliary spasm.

Skin and subcutaneous tissue disorders: rashes, urticaria, pruritus, sweating.

Musculoskeletal and connective tissue disorders: muscle fasciculation or rigidity.

Renal and urinary disorders: difficulty with micturition, ureteric spasm or retention.

Reproductive system and breast disorders: decreased libido or potency.

General disorders and administration site conditions: drug withdrawal syndrome (uncommon)

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.

4.9 Overdose

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

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.

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 if more than
2.5 mg/kg (adults and children) has been ingested.

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.

5.1 Pharmacodynamic properties

Codeine depresses the cough reflex, partly by a direct effect on a cough centre in the medulla; the exact mechanism is not entirely clear. It has been suggested that the usual doses of opioids produce their major effect on the patient's subjective reactions to the cough, rather than on the frequency and intensity of coughing.

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 phosphate is absorbed from the gastro-intestinal tract, it is metabolised by O- and N-Demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.
Ingestion of codeine phosphate produces peak plasma - codeine concentrations in about one hour. The plasma half-life has been reported to be between 2½ and 4 hours after ingestion.

5.3 Preclinical Safety Data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid Monohydrate
Purified Water
Lemon Oil Terpeneless
Ethanol (96%)
Benzoic Acid Solution (contains benzoic acid (E210) and propylene glycol (E1520))
Invert Syrup
Quinoline Yellow (E104)
Yellow Dye Sunset (E110)
Syrup

6.2 Incompatibilities

Codeine phosphate is incompatible with bromides, iodides and salts of heavy metals.
It is incompatible with phenobarbitone sodium, forming a codeine-phenobarbitone complex.

6.3 Shelf life

36 months unopened

6.4 Special Precautions for Storage

Protect from light.
Store below 25°C.

6.5 Nature and contents of container

200ml: Amber glass bottle with white 28mm child-resistant cap with tamper evident band and EPE/Saranex liner.

6.6 Instruction for Use/Handling and Disposal

None.

7. MARKETING AUTHORISATION HOLDER

L.C.M. LIMITED
Linthwaite Laboratories
Huddersfield
HD7 5QH

8. MARKETING AUTHORISATION NUMBER(S)

PL 12965/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

21.7.1993

10 DATE OF REVISION OF THE TEXT

18/03/2024