SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Crescent Tablets 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate 30 mg per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White normal convex tablets.

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).

4.2 Posology and method of administration

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 240mg.

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 240mg 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).

ROUTE OF ADMINISTRATION: Oral

4.3 Contraindications

Hypersensitivity to codeine or other opioid analgesics or to any of the excipients.

Acute respiratory depression and obstructive airways disease.

Diarrhoea due to pseudomembranous colitis or poisoning.

Severe hepatic dysfunction.

Where there is a risk of paralytic ileus.

Raised intracranial pressure or head injury.

Comatose patients

Acute alcoholism

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

Not recommended for use in patients with acute asthma. Use with caution or in reduced doses in asthma and decreased respiratory reserve. (see 4.3 Contraindications).

Codeine phosphate should be avoided, or the dose reduced, in patients with hepatic or renal impairment (see 4.3 Contraindications, liver disease).

Codeine phosphate should be given in reduced doses or with caution to:

Debilitated patients, elderly patients, adrenocortical insufficiency, prostatic hypoplasia, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, hypothyroidism, convulsive disorders or myasthenia gravis.

However, these conditions should not necessarily be a deterrent to use in palliative care. Discontinuation should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms.

Use with caution in those with a history of drug abuse.

Alcohol should be avoided whilst under treatment with codeine.

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, shallow breathing, small pupils, nausea, vomiting, 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% to 2%

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.

Opioid analgesics should be avoided in patients with biliary tract disorders or used in conjunction with an antispasmodic.

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.

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.

The leaflet will state in

Section 2 “Before taking your medicine”:

'**Pregnancy and breast-feeding**'

If you are pregnant or planning to become pregnant then consult your doctor or pharmacist before taking these medicines.

Do not take codeine while you are breastfeeding. Codeine and morphine passes into breast milk.

'**Warnings and precautions**'

Codeine is transformed to morphine in the liver by an enzyme. Morphine is the substance that produces pain relief. Some people have a variation of this enzyme and this can affect people in different ways. In some people, morphine is not produced or produced in very small quantities, and it will not provide enough pain relief. Other people are more likely to get serious side effects because a very high amount of morphine is produced. If you notice any of the following side effects, you must stop taking this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of codeine with antidiarrhoeal and antiperistaltics such as difenoxin, atropine, kaolin, pectin, belladonna alkaloids, opium preparations and loperamide, may increase the risk of severe constipation and central nervous system depression.

Concurrent administration of codeine with antihypertensive agents especially ganglionic blockers such as guanethidine, diuretics, hypotension producing medication may potentiate the hypotensive effect and increase risk of orthostatic hypotension.

Concurrent administration of codeine with other medications with antimuscarinic action may lead to an increased risk of severe constipation and may lead to paralytic ileus and/or urinary retention.

Domperidone and metoclopramide:

Codeine antagonises the effect of metoclopramide or domperidone on gastrointestinal activity.

The depressant effects of opioid analgesics are enhanced by other CNS depressants such as:

Alcohol – enhanced hypotensive, sedative effect and respiratory depression.

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.

Antihistamines – concomitant administration of codeine and antihistamines with sedative properties may cause increased CNS depression and/or respiratory depression and/or hypotension.

Anxiolytics or hypnotics – enhanced sedative effect.

Antidepressants – The depressant effects of opioid analgesics may be enhanced by tricyclic antidepressants

Antipsychotics – enhanced hypotensive, sedative effect.

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.

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

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.

Administration with moclobemide may cause CNS excitation or depression (hypertension or hypotension).

Ulcer-healing drugs - Cimetidine may inhibit the metabolism of codeine, resulting in increased plasma concentrations.

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 of codeine during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate. Administration of codeine during labour may depress respiration in the neonate. Opioid analgesics may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.

Lactation:

Codeine is contraindicated in women during breastfeeding (see section 4.3).

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 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 produces sedation and may also cause changes in vision, including blurred or double vision therefore treatment may impair ability to drive and use machines. 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. 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.

In therapeutic doses, codeine is much less liable than morphine to produce adverse effects.

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.

<u>Immune system disorders</u>

Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate; fever, splenomegaly and lymphadenopathy also occurred.

<u>Endocrine disorders</u>

Hyperglycaemia.

Metabolism and nutrition disorders

Anorexia.

Psychiatric disorders

Mental depression, hallucinations and nightmares, restlessness, confusion, mood changes, euphoria, dysphoria.

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.

Rare cases of sensorineural hearing loss have been reported with codeine and codeine containing products.

Cardiac disorders

Bradycardia, tachycardia, palpitations.

Vascular disorders

Postural hypotension, facial flushing. Large doses produce hypotension.

Respiratory, thoracic and mediastinal disorders

Dyspnoea. Large doses produce respiratory depression.

Gastrointestinal disorders

Pancreatitis, nausea and vomiting, constipation, dry mouth, stomach cramps.

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

Allergic reactions such as skin rashes, urticaria, Sweating, pruritus and facial oedema.

Musculoskeletal, connective tissue and bone disorders

Uncontrolled muscle movements. Muscle rigidity may occur after high doses.

Renal and urinary disorders

Difficulty with micturition, 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.

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

The effects in over dosage 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. Dry mouth, sweating and facial flushing are other symptoms of overdose. High doses of codeine may produce sedation or excitement and, in children, convulsions 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 sustained release preparation has been taken.

Naloxone may be given according to the following dose regimens:

Intravenous Injection:

0.8-2mg repeated at intervals of 2-3 minutes to a maximum of 10mg.

Child: 10µg/kg and, if no response, subsequent doses of 100µg/kg.

Subcutaneous or Intramuscular Injection:

As for intravenous injection but only if the i.v. route is not feasible. The onset of action is slower with s.c. or i.m. injection.

Continuous intravenous infusion:

2mg diluted in 500ml of intravenous infusion solution at a rate adjusted according to the patient's response

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Codeine is much less potent as an analgesic as compared with morphine and has only mild sedative effect.

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 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

Maize starch

Lactose

Talc

Magnesium stearate

Sodium laurilsulfate (not present in the 15mg tablet)

6.2 Incompatibilities

None.

6.3 Shelf life

3 years for opaque plastic containers and amber glass bottles.

3 years for blisters.

6.4 Special precautions for storage

Keep out of the reach of children. Protect from heat, light and moisture.

6.5 Nature and contents of container

Codeine Phosphate Crescent Tablets 30 mg are packed in the following pack types and pack sizes.

Opaque plastic containers (securitainers) fitted with plastic caps for all pack sizes.

Amber glass bottles for all pack sizes.

Opaque plastic container composed of either high density polypropylene or high density polyethylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene for all pack sizes (28, 30, 42, 50, 56, 84, 100, 112, 250, 500, 1000 and bulk) with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler.

Blister packs of aluminium opaque/PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 42, 56, 84 and 112.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Crescent Pharma International Limited
260, Triq San Albert
Gzira GZR 1150
Malta

8. MARKETING AUTHORISATION NUMBER(S)

MA1317/01601

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th August 2019

10. DATE OF REVISION OF THE TEXT

08/2019