Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codant 30 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Codeine Phosphate Hemihydrate 30 mg (equivalent to 23.4 mg Codeine).

Excipient(s) with known effect
Also contains 43 mg of lactose monohydrate (equivalent to 40.9 mg lactose).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White, circular biconvex tablets of 5.5mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1) Management of mild to moderate pain.

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.

2) As an anti-tussive for non-productive cough.

4.2 Posology and method of administration

Posology

Adults
The usual dose is 30mg (one tablet), repeated 6 hourly as required.

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 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.

Elderly
A reduced dosage may be necessary.

Paediatric population
Children aged 12 years to 18 years:
"The recommended codeine dose for children 12 years and older should be 30 to 60 mg every 6 hours when necessary up to a maximum dose 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).
Dosage needs to be adjusted according to the severity of pain and the response of the patient.

Method of administration
Codant tablets are for oral administration only.

Treatment goals and discontinuation
Before initiating treatment with Codant tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Codant tablets should not be used longer than necessary.

4.3 Contraindications

• Hypersensitivity to the active substance, other opioids or to any of the excipients listed in section 6.1.
• Children under 12 years of age.
• Patients who have taken MAOIs within 14 days.
• Conditions associated with raised intracranial pressure, and in head injury and coma
• Internal obstruction.
• Respiratory depression.
• Hepatic failure
• Following biliary surgery
• Obstructive airways disease e.g. emphysema
• Asthma – Opioids should not be administered during an asthma attack
• Acute alcoholism
• Risk of paralytic ileus
• 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

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

_ Impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack)
_ 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
_ 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
_ Gall bladder disease or gall stones – opioids may cause biliary obstructions
Avoid in biliary disorders
_ Gastro intestinal surgery – use with caution after recent GI surgery as codeine may alter GI mobility
_ Urinary tract surgery –following recent surgery patient 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
_ Elderly patients may metabolize and eliminate opioid analgesics more slowly than younger patients, a reduced dose is recommended in elderly patients.

Agents which inhibit intestinal motility have been reported to induce toxic megacolon in some patients with ulcerative colitis.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Codant tablets. Repeated use of Codant tablets can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Codant tablets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Codant tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Codeine is metabolized by liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme anadequate analgesic effect willnot be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultrarapid metabolizer 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 nausea, vomiting, confusion, 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 metabolizer 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%

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs and gabapentinoids:

Concomitant use of codeine and sedative medicines such as benzodiazepines or related drugs and gabapentinoids (gabapentin and pregabalin) may result in profound sedation, respiratory depression, hypotension, coma or death. Because of these risks, concomitant prescribing with these medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe codeine concomitantly with sedative medicines or gabapentinoids, 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).

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Hyperalgesia
As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Hepatobiliary disorders
Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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 metabolizers in their ability to metabolize 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.

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

4.5 Interaction 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 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 concentration
_ 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

Sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids:
The concomitant use of (Codant) with sedative medicines (such as benzodiazepines or related drugs) and gabapentinoids (gabapentin and pregabalin) may result in profound sedation, respiratory depression, hypotension, coma or 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
There is inadequate evidence of the safety of codeine in human pregnancy and administration of the drug during pregnancy should be considered only if the potential benefit justifies the potential risk to the foetus.

Opioid analgesics cross the placenta and newborn infants should be observed closely for signs of respiratory depression if the mother has received codeine during labour. Use of codeine during pregnancy may lead to withdrawal symptoms in neonates. Should such signs/symptoms be noted in mother or baby, the mother should immediately stop taking all codeine-containing medicines and seek medical advice.

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 should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine 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 metabolites 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*.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Codeine may cause sedation and dizziness and patients should be advised not to drive or to operate machinery if affected.

4.8 Undesirable effects

Undesirable effects are especially likely to occur at treatment onset or at dose increase.
The undesirable effects are listed below by organ class and the following frequency convention:
Not known – cannot be estimated from the available data.

System organ class	Undesirable effects
Psychiatric disorders	Confusion, Hallucinations, Mood change, CNS excitation (restlessness/excitement), depression mental, nightmares, dependence, dysphoria
Nervous system disorders	Drowsiness, dizziness, convulsions, headache, Increased intracranial pressure
Eye disorders	Miosis, blurred or double vision
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Bradycardia, palpitations, tachycardia
Vascular disorders	Flushed face, hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Respiratory depression with larger doses, difficulty breathing
Gastrointestinal disorders	Constipation (too constipating for long-term use), nausea, vomiting, dry mouth, pancreatitis
Hepatobiliary disorders	Biliary spasm, sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus, sweating increased, redness
Musculoskeletal and connective tissue disorder	Muscle rigidity
Renal and urinary disorders	Urethral spasm, antidiuresis, urinary retention
Reproductive system and breast disorders	Decrease in libido and potency
General disorders and administration site conditions	Withdrawal effects: abrupt withdrawal precipitates a withdrawal syndrome* Malaise, tiredness, tolerance, hypothermia

*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. Symptoms of restlessness and irritability may result when treatment is then stopped.

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.
_ Prolonged use of a painkiller for headaches can make them worse

Drug dependence
Repeated use of Codant tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 HPRA Pharmacovigilance,
Website: www.hpra.ie

4.9 Overdose

Symptoms:
Serious overdosage with codeine is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils and respiratory depression is strongly suggestive of opiate poisoning.

Management:
In cases of recent overdosage, the stomach should be emptied by aspiration and lavage. A patent airway should be maintained and assisted or controlled ventilation should be instituted if required. The narcotic antagonist naloxone hydrochloride may be administered to counteract significant respiratory depression if it occurs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opoids; ATC code: N02A A59

Mechanism of action
Codeine is a centrally acting analgesic. The anti-tussive activity of codeine is probably due to its depressant effect on the medullary cough centre in the brain.

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

Absorption
Codeine phosphate is readily absorbed from the gut.

Biotransformation and Elimination
The drug is metabolized in the liver and is excreted through urine as conjugates. The plasma half –life is 3-4 hours.
Codeine crosses the blood-brain and placental barriers and detectable amounts have been reported to occur in the breast milk.

5.3 Preclinical safety data

No relevant information other than that which is reported in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Anhydrous Silica
Lactose Monohydrate
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original container in order to protect from light.

6.5 Nature and contents of container

Polypropylene tablets containers with tamper evident polyethylene caps.

Pack size: 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
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8 MARKETING AUTHORISATION NUMBER

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