SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Tablets 15mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains codeine phosphate 15mg.

3. PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an analgesic in mild to moderate pain, as an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.
Codeine is indicated 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 Phosphate Tablets 15 mg are not indicated for children 0-18 years old.

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.

<u>In mild to moderate pain:</u>

Adults and the elderly: 30 mg to 60 mg every 6 hours when necessary, to a maximum of 180 mg daily.

As an anti-tussive:

Adults and the elderly: 15 mg to 30 mg, 3 or 4 times daily.

For the symptomatic treatment of chronic diarrhoea:

Adults and the elderly: 15 mg to 60 mg every 6 hours, to a maximum of 180 mg daily.

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.

Method of administration: Oral

4.3 Contraindications

- Respiratory depression and liver failure.
- 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

Prolonged use of high doses has produced morphine-like dependency. Avoid when there is a history of asthma, hepatic or renal impairment, or of drug abuse. The risk benefit of continued use should be assessed regularly by the prescriber.

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%
Nothern European	1% to 2%

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Codeine 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 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).

4.5 Interactions with other medicinal products

Forms codeine-phenobarbital complex with phenobarbital sodium and crystals of codeine periodide with potassium iodide. Alcohol can enchance the sedative and hypotensive effect of codeine. Codeine may enchance the sedative effects of anxiolytics and hypnotics. Codeine may also antagonise the gastro-intestinal effects of metoclopramide and domperidone.

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

Not recommended during pregnancy.
Codeine should not be used 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.

4.7. Effects on ability to drive and use machines

In combination with alcohol has a deleterious effect on driving.

4.8 Undesirable effects

Constipation, tolerance, dependence, sedation, dizziness, and nausea may occur; may enhance the effect of alcohol. Rash, urticaria, pruritus and headache have also been reported.

Regular prolonged use of codeine/ DHC is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is stopped.

Prolonged use of painkiller for headaches can make them worse.

4.9 Overdose

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.

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

The action of codeine is largely that of morphine from which it is derived i.e. it is a CNS suppressant.

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 metabolised in the liver and is excreted in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered codeine is demethylated to form morphine; traces of free morphine can be found in the urine after therapeutic doses of codeine.

5.3. Preclinical safety data

There are no preclinical safety data of relevance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, starch, magnesium stearate and sodium starch glycollate.

6.2. Incompatibilities

Forms codeine-phenobarbitone complex with phenobarbitone sodium and crystals of codeine periodide with potassium iodide.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

Securitainers: Pack sizes: 28, 30, 50, 100 and 500.

Blister packs: Aluminium/PVC/PVdC blister packs Pack size 28

6.6. Instructions for use/handling

Not applicable

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Frimley Business Park
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Camberley
Surrey
GU16 7SR
UK

8. MARKETING AUTHORISATION NUMBER

PL 04416/0211

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/05/2008

10 DATE OF REVISION OF THE TEXT

02/03/2019