SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine phosphate 30 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of codeine phosphate.

Excipient(s) with known effect:
Each tablet contains 38.46 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White circular normal biconvex tablets, embossed with R115.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Recommended Uses: As an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.

4.2 Posology and method of administration

Posology
For oral administration.

Treatment goals and discontinuation
Before initiating treatment with Codeine phosphate, treatment duration and treatment goals, 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).

The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

As an analgesic:

Adults: 30-60mg every four hours, when necessary to a maximum 240mg daily. Children: Not applicable.

As an anti-tussive:

Adults:
15-30mg three or four times daily.
Paediatric population
Not recommended for children.

For the symptomatic treatment of chronic diarrhoea.:

Adults: 10-60mg every four to six hours.
Children: Not applicable.

In general dosage should be reduced in elderly patients.
Codeine phosphate should not be used longer than necessary.

4.3 Contraindications

- hypersensitivity to the codeine phosphate, other opioid analgesics or any other of the excipients listed in section 6.1.
- patients with respiratory depression, liver disease, raised intracranial pressure, head injuries, acute alcoholism and diarrhoea associated with either pseudomembranous colitis or poisoning.

4.4 Special warnings and precautions for use

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 Codeine phosphate. Repeated use of Codeine phosphate 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 Codeine phosphate 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).
The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.
For patients who experience signs and symptoms of OUD, and/or exibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.
Prolonged use of high doses has produced drug dependence of the Morphine type. Codeine should be used with caution in patients with a history of drug dependence, in asthmatics and in patients with renal impairment. Care should be taken if the patient has hypotension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, acute abdominal conditions, recent GI surgery, gallstones, myasthenia gravis, history of cardiac arrhythmias or convulsions.
The risk-benefit of continued use should be assessed regularly by the prescriber.
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.
Codeine Phosphate Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
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.

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic

effects. Estimates indicate that up to 7% of the caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low 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. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers.

The leaflet will state in the "Pregnancy and breast-feeding" subsection of section 2 "Before taking your medicine":

Usually it is safe to take "brand name" while breast feeding as the level of the active ingredients of this medicine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice; feeling sick, vomiting, constipation, decreased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

4.5 Interaction with other medicinal products and other forms of interaction

Forms codeine-phenobarbital complex with phenobarbital sodium and crystals of codeine periodide with potassium iodide.
Codeine is known to interact with other CNS depressants (e.g. alcohol, sedatives, hypnotics), other antidiarrhoeal agents, neuromuscular blocking agents, antihypertensives, cimetidine and monoamine oxidase inhibitors (also within two weeks of stopping treatment with MAOI).
The concomitant use of Codeine phosphate with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).
Codeine also interferes with some laboratory tests e.g. plasma amylase, lipase, bilirubin.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
Not recommended during pregnancy due to neonatal withdrawal symptoms and impaired effect of foetus.
Breast-feeding
At normal therapeutic doses codeine and its active metabolites 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.

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

In combination with alcohol, it has a deleterious effect on driving.

4.8 Undesirable effects

Tolerance and dependence, sedation, dizziness, nausea and constipation commonly occurs. May enhance the effect of alcohol. Other undesirable effects are sweating, facial flushing, dry mouth, blurred or double vision, hypotension, malaise, headache, anorexia, bradycardia, allergic reactions (itch, skin rash, facial oedema) and difficulty in micturition. Rare side effects are convulsions, hallucinations, nightmare, uncontrolled muscle movements and rigidity, mental depression and stomach cramps.

Gastrointestinal disorders

Not known: pancreatitis

Hepatobiliary disorders

Not known: sphincter of Oddi dysfunction

Drug dependence

Repeated use of Codeine phosphate 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).

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.

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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

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 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opium alkaloids and derivatives, codeine

ATC code: R05DA04

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

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

Animal work suggested that the analgesic activity of Codeine was not affected by Acetylation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Starch
Magnesium Stearate
Sodium Starch Glycolate

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years: Polypropylene tamper-evident containers.

2 years: Blister strips.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Polypropylene tamper-evident containers: 1000, 500, 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets

Blister strips: 100, 90, 80, 70, 60, 50, 40, 30, 28, 20 and 10 tablets.

Not all pack types or sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
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Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

PL 28444/0164

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/09/2011

10 DATE OF REVISION OF THE TEXT

23/02/2026