

CODEINE PHOSPHATE INJECTION 60MG IN 1ML

PL 13079/0010

UKPAR

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CODEINE PHOSPHATE INJECTION 60MG IN 1ML

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted South Devon Healthcare a Marketing Authorisation (licence) for the medicinal product Codeine Phosphate Injection 60mg in 1ml (product licence number 13079/0010) on 14 February 2007. This medicine is available by prescription for use in pain relief.

Codeine Phosphate Injection 60mg in 1ml contains the active ingredient codeine phosphate, which belongs to a group of medicines called the opioids. Opioids mimic the effect of endorphins, chemicals that we produce naturally that reduce pain. They work by combining with certain receptors in the brain, blocking the transmission of pain signals.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Codeine Phosphate Injection 60mg in 1ml outweigh the risks, hence a Marketing Authorisation has been granted.

CODEINE PHOSPHATE INJECTION 60MG IN 1ML

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Codeine Phosphate Injection 60mg in 1ml (PL 13079/0010) on 14 February 2007. The product is a prescription-only medicine (POM).

This is a standard abridged bibliographic application for a sterile solution of codeine phosphate hemihydrate presented in 1ml glass ampoules and administered by intramuscular injection.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Codeine phosphate is a white, crystalline powder or small colourless crystals, freely soluble in water.

A Certificate of Suitability for the active substance has been issued. This means that the codeine phosphate used in this product complies with the monographs of the European Pharmacopoeia. Some additional controls are carried out, as appropriate for this source of active substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active codeine phosphate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analyses, demonstrating compliance with the current European Pharmacopoeia, are provided.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer.

Appropriate stability data have been generated for the active substance.

DRUG PRODUCT

Composition

The formulation is a simple solution of codeine phosphate and water for injections. Helium is used to degas the solution and oxygen-free nitrogen is used to give an inert gas cover over the solution in the ampoule.

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of helium gas, which complies with the British Pharmacopoeia (BP) monograph (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

Manufacture

Satisfactory detail of the manufacturing process has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation is demonstrated by consistent results on analysis of the finished product and by validation of autoclaves.

It is declared that there are no materials of animal or human origin used in the manufacturing processes.

Finished product specification

The finished product specification is appropriate and is based on the BP monograph for codeine phosphate injection.

Test methods have been described satisfactorily and have been adequately validated.

Batch data demonstrate compliance with the specification. The BP Chemical Reference Substance is used as the Reference Standard.

Container Closure System

The product is packed into clear colourless type I glass ampoules, containing 1 ml of solution in packs of 10 ampoules in a cardboard carton. Technical specifications have been provided. The ampoules comply with DIN-ISO 9187-1 and Ph Eur specifications. Details of the sampling and testing of packaging components have been provided and are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “For single dose use only, discard any unused solution immediately after first use.”

Product Literature

All product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) is satisfactory for this product.

Conclusions and advice

Grant of a licence is recommended.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none is required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Codeine Phosphate Injection 60mg in 1ml are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

The efficacy of codeine phosphate has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been demonstrated for Codeine Phosphate Injection 60mg in 1ml in the therapeutic indications proposed. The risk benefit is therefore considered to be positive.

CODEINE PHOSPHATE INJECTION 60MG IN 1ML

PL 13079/0010

STEPS TAKEN FOR ASSESSMENT

| | |
|---|--|
| 1 | The MHRA received the marketing authorisation application on 26 November 2004 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the application valid on 24 January 2005 |
| 3 | Following assessment of the application the MHRA requested further information on the quality dossier on 11 May 2005 and 16 March 2006. The applicant responded to the MHRA's requests, providing further information on 15 November 2005 and 11 July 2006 |
| 4 | The MHRA requested further information on the quality dossier on 28 July 2006. The applicant responded to the MHRA's requests, providing further information on 27 September 2006 |
| 5 | The application was determined on 14 February 2007 |

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate Injection 60mg in 1ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine Phosphate 60mg in 1ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The product is a clear, pale straw colour solution, visibly free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The relief of mild to moderate pain.

4.2 Posology and method of administration

For intramuscular use only.

Adults, elderly and debilitated patients

30 - 60mg every 4 hours when necessary.

Hepatic impairment

Codeine Phosphate injections is contraindicated in patients with hepatic impairment (see Section 4.3).

Renal impairment

The dosage for patients with renal impairment should be adjusted according to the table below.

| Glomerular filtration rate (mL/minute) | Dose |
|---|-----------------------------------|
| 20-50 | Dose as for normal renal function |
| 10-20 | 75% of normal dose |
| <10 | 50% of normal dose |

Children over 1 year

1 year to 12 years: 500 micrograms/kg to 1mg/kg four to six times daily.

Maximum daily dose in the 12-18 year old age group is 240mg.

Children under 1 year

Codeine Phosphate Injection is not to be used in children below 1 year due to insufficient data on safety and efficacy in this age group.

4.3 Contraindications

Hypersensitivity to the active substance.

Codeine Phosphate Injection is not to be used in children below 1 year due to insufficient data on safety and efficacy in this age group.

Codeine Phosphate Injection is contraindicated in patients with hepatic impairment.

As codeine reduces peristalsis, increases tone in the bowel and can raise colonic pressure, it should not be used in diverticulitis, after bowel surgery or in those with acute colitis.

4.4 Special warnings and precautions for use

Use with care in patients with pre-existing respiratory depression, as opioids can further depress respiratory function.

Use with care in head injury as opioids can depress respiratory function, which can then complicate the situation (carbon dioxide retention causes dilatation of intracranial vessels and thus cerebral oedema).

Use with care in patient with hypovolaemia as this may be exacerbated with codeine.

Repeated administration of codeine phosphate may induce tolerance to the drug and morphine-type dependence.

Codeine potentiates the central depressive effects of central nervous system depressants including alcohol.

Patients should therefore avoid alcohol whilst taking codeine.

Codeine may cause drowsiness. If affected, patients should not drive or operate machinery.

Do not use if the solution is darker than pale straw.

Do not use if visible particles are present.

Once opened the product should be used immediately and any unused drug discarded.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing codeine phosphate injection to patients taking drugs which also cause central nervous system depression; or induce liver enzymes (examples include nefopam, carbamazepine, rifampicin, quinidine, secobarbital) as this may reduce the efficacy of the drug.

Patients should avoid alcohol whilst taking codeine (see Section 4.4).

4.6 Pregnancy and lactation

There are no adequate data from the use of codeine in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy and embryofetal development (see Section 5.3). The potential risk for humans is unknown. Codeine Phosphate Injection should not be used in pregnancy, in particular during the later stages, unless the clinical benefit outweighs the potential risk.

Codeine is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of Codeine Phosphate Injection are administered to breast feeding women. The breast fed infants of those taking codeine should be observed for respiratory depression and sedation.

4.7 Effects on ability to drive and use machines

Codeine Phosphate Injection has a minor or moderate influence on the ability to drive and use machines. Codeine may cause drowsiness. If affected, patients should not drive or operate machinery (see Section 4.4).

4.8 Undesirable effects

The following adverse events are from published literature and frequencies are not known.

Psychiatric disorders

Hallucination, mood altered, restlessness

Nervous system disorders

Somnolence

Eye disorders

Miosis

Ear and Labyrinth disorders

Vertigo

Cardiac disorders

Bradycardia, palpitations

Vascular disorders

Flushing, orthostatic hypotension

Gastrointestinal disorders

Constipation, dry mouth, nausea, vomiting

Hepatobiliary disorders

Biliary colic

Skin and subcutaneous tissue disorders

Hyperhidrosis

Renal and urinary disorders

Dysuria, ureteral spasm

General disorders and administration site conditions

Hypothermia

4.9 Overdose

In acute overdose, respiratory depression and hypotension may be observed. Circulatory failure and deepening coma may also be observed. The respiratory failure may cause convulsions. Respiratory failure must be guarded against. If respiration is dangerously depressed Naloxone should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opium alkaloids and derivatives, ATC code: R05D A04

Codeine phosphate is an opioid analgesic. Codeine produces its analgesic effects by binding to mu-receptors. Codeine also binds weakly to kappa-receptors, which mediate analgesia, meiosis and sedation. Codeine resembles morphine in possessing analgesic, anti-tussive and antidiarrhoeal properties. However, the affinity of codeine for the opiate receptor is low and it is not effective against severe pain.

5.2 Pharmacokinetic properties

Absorption: After intramuscular injection, peak plasma concentrations occur in about 30 minutes and the half-life is approximately 3 hours. The maximum plasma concentrations after normal therapeutic doses are in the range of 100-300 micrograms/L.

Distribution: The volume of distribution is approximately 3.6L/kg. Codeine enters the tissues rapidly and is concentrated in the kidney, lung, liver and spleen. The bulk of the total drug is in the skeletal muscle. The brain does not accumulate high levels of codeine. Within the brain, 80% or more is associated with opioid receptors which are especially concentrated in the caudate nucleus, amygdala and peri-aqueductal grey matter of the hypothalamus, mid brain and medial thalamus.

Biotransformation: The majority of codeine undergoes hepatic metabolism by glucuronidation to codeine-6-glucuronide, N-demethylation to norcodeine and o-demethylation to morphine.

Elimination: After an intramuscular dose, approximately 15-20% of the dose is excreted unchanged in acid urine in 24 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

For single dose use only, discard any unused solution immediately after first use.

6.4 Special precautions for storage

Do not store above 25°C.

Keep ampoules in the original outer carton.

6.5 Nature and contents of container

Clear colourless type I glass ampoules containing 1ml of solution in packs of 10 ampoules in a cardboard carton.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

South Devon Healthcare

Torbay PMU

Long Road

Paignton

Devon TQ4 7TW

8 MARKETING AUTHORISATION NUMBER(S)

PL 13079/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/02/2007

10 DATE OF REVISION OF THE TEXT

25/09/2007

PATIENT INFORMATION LEAFLET

**SOUTH DEVON
HEALTHCARE**

PATIENT INFORMATION LEAFLET

CODEINE PHOSPHATE INJECTION

60MG IN 1ML

PLEASE READ THIS LEAFLET CAREFULLY. IF YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR OR PHARMACIST. KEEP THIS LEAFLET IN A SAFE PLACE, YOU MAY WISH TO READ IT AGAIN.

ABOUT CODEINE PHOSPHATE INJECTION 60MG IN 1ML

Codeine Phosphate Injection 60mg in 1ml contains 60mg of codeine phosphate as the active ingredient. It is presented in 1ml ampoules for single dose use only.

Codeine Phosphate Injection 60mg in 1ml also contains the following inactive substance:

Water for injections.

The manufacturer and marketing authorisation holder is:

South Devon Healthcare
Torbay PMU
Long Road
Paignton
Devon
TQ4 7TW

Codeine Phosphate Injection 60mg in 1ml is a solution for injection for intramuscular use and is used for:

The relief of mild to moderate pain.

WHEN CODEINE PHOSPHATE INJECTION 60MG IN 1ML SHOULD NOT BE USED

- Should not be given if you have liver disease
- Should not be given to children who are under 1 year
- Should not be given if you have diverticulitis or acute colitis
- Should not be given after bowel surgery

WHEN CODEINE PHOSPHATE INJECTION 60MG IN 1ML SHOULD BE USED WITH CARE

- Use with care if you have a head injury
- Use with care if you have hypovolaemia (decreased amount of blood in the body)
- Use with care if you already have shallow breathing

BEFORE USING CODEINE PHOSPHATE INJECTION 60MG IN 1ML

- Please tell your doctor if you are taking any other medication
- Please tell your doctor if you are pregnant or breast feeding

Codeine Phosphate Injection 60mg in 1ml should be used with caution in patients who are:

- Pregnant

- Breast feeding
- Very young
- Very elderly

Do not use Codeine Phosphate Injection 60mg in 1ml if:

- Visible particles are present
- The solution is darker than pale straw

USING CODEINE PHOSPHATE INJECTION 60MG IN 1ML

Codeine Phosphate Injection 60mg in 1ml is a solution for intramuscular injection only. In adults, elderly and debilitated patients 30-60mg every 4 hours when necessary may be administered. In children aged 1-12 years, 500 micrograms/kg to 1mg/kg four to six times daily may be administered. The maximum daily dose in the 12-18 year old age group is 240mg.

Alcohol should be avoided whilst taking codeine.

WHAT TO DO IN CASE OF OVERDOSE

In acute overdosage, respiratory depression and hypotension (low blood pressure) may be observed. Circulatory failure and deepening coma may also be observed. The respiratory failure may cause convulsions. Respiratory failure should be guarded against; however, if respiration becomes dangerously depressed naloxone should be used.

SIDE EFFECTS OF CODEINE PHOSPHATE INJECTION 60MG IN 1ML

Codeine phosphate may cause nausea,

vomiting, constipation, drowsiness, difficulty with passing water, spasm of the bile duct or ureter, dry mouth, sweating, facial flushing, giddiness, slow heart rate, palpitations, feeling faint on standing up, low body temperature, restlessness, imagining things, mood changes, pinpoint pupils. If you notice these or any other unwanted side effects, please tell your doctor immediately.

Repeated administration of codeine phosphate may induce a tolerance to the drug and morphine-type dependence.

**STORING CODEINE PHOSPHATE
INJECTION 60MG IN 1ML**

- The product has an expiry date stated on the ampoule and carton. Before use the doctor or nurse will check the product has not passed this date and that the injection does not show signs of deterioration.
- Do not store above 25°C.
- Store this medicine in a safe place where children cannot see it or reach it.
- Keep the container in the original outer carton.

**PL 13079/0010
PIL/9/1**

Date of leaflet preparation: October 2003

LABELLING

