

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Codeine Phosphate Tablets (PSM)

15 mg, 30 mg & 60 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Codeine Phosphate Hemihydrate BP 15 mg

Codeine Phosphate Hemihydrate BP 30 mg

Codeine Phosphate Hemihydrate BP 60 mg

Codeine phosphate hemihydrate is obtained from opium or made by methylating morphine. It occurs as odourless colourless crystals or white crystalline powder.

The molecular formula of codeine phosphate is $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ and the molecular weight 406.4.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral – tablet

Presentation

Codeine Phosphate Tablets (PSM) are white, biconvex circular tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine phosphate is indicated for:

- the relief of mild to moderate pain (including pain associated with terminal illness, post-operative pain, headache),
- the relief of symptoms of diarrhoea (except diarrhoea caused by poisoning).

4.2 Dose and method of administration

Adults:

Codeine phosphate may be given orally in doses of 15 mg – 60 mg every 4 – 6 hours as needed.

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If these doses fail to relieve pain, larger doses rarely succeed and may give rise to restlessness and excitement.

The maximum daily dose in adults should not exceed 300 mg.

Paediatric:

Do not use in children aged less than 12 years (see sections 4.3 and 4.4).

The usual paediatric dose is 0.5 mg per kg of body weight, every 4 to 6 hours as needed. The total dose should not exceed 240 mg in 24 hours. The duration of treatment should not normally exceed 3 days.

4.3 Contraindications

Codeine phosphate is contraindicated in:

- Known hypersensitivity to codeine, other opioids or any component of the tablets
- Acute respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion
- Obstructive airways disease
- Acute alcoholism
- Head injuries and conditions in which intracranial pressure is raised
- Patients at risk of paralytic ileus
- Hepatic failure
- Acute asthma attack
- Heart failure secondary to chronic lung disease
- Diarrhoea associated with pseudomembranous colitis or caused by poisoning
- Patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment
- Children aged less than 12 years (see section 4.4)
- Adolescents aged less than 18 years for pain following surgery to remove tonsils or adenoids (see section 4.4)
- Adolescents aged less than 18 years in whom respiratory function might be compromised (see section 4.4)
- Adolescents aged less than 18 years for symptomatic relief of cough and cold (see section 4.4)
- Women who are breastfeeding (see section 4.4)

4.4 Special warnings and precautions for use

The following patients may be more susceptible to the effects of codeine. The lowest effective dose for the shortest period of time should be prescribed. Signs of toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, confusion, shallow breathing and even coma. If symptoms of toxicity are present, codeine should be stopped immediately and medical advice

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sought.

- recent tonsillectomy, adenoidectomy or throat surgery
- hypothyroidism
- adrenocortical insufficiency e.g. Addison's disease
- impaired kidney or liver function
- prostatic hypertrophy
- shock/hypotension
- myasthenia gravis
- convulsions / convulsive disorders
- gall bladder disease or gall stones
- recent gastro-intestinal surgery
- urinary tract surgery
- reduced respiratory function or history of asthma
- obstructive bowel disorders – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment

Hypersensitivity

Maculopapular rash, fever, splenomegaly and lymphadenopathy have been seen as part of a codeine hypersensitivity reaction.

Dependence

Taking codeine regularly for a long time can lead to addiction. Stopping treatment can result in withdrawal symptoms.

Prolonged use of high doses of codeine has produced dependence of the morphine type in a very small proportion of users. Codeine produces less euphoria and sedation than morphine and is not a completely satisfactory substitute for morphine in morphine addicts.

Regular use of analgesics for headache can result in an overuse syndrome.

Withdrawal

Abrupt withdrawal precipitates a withdrawal syndrome. 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. These effects can also occur in neonates exposed to codeine *in utero* (see use in pregnancy).

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

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Withdrawal symptoms develop more slowly than with morphine and are milder.

CYP2D6 Genetic polymorphism

Codeine may be partially metabolised by CYP2D6 to morphine. Patients who are deficient in or lacking this enzyme cannot convert codeine to morphine and therefore will not obtain adequate analgesic effects. Conversely, some patients are able to convert codeine to morphine more rapidly and completely. Patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects or opioid toxicity, even at low doses. Adverse effects range from less serious symptoms such as nausea, vomiting, constipation, 'pin-point' pupils and dizziness or drowsiness, through to life-threatening symptoms such as shallow breathing, slow heart rate, confusion, hallucinations, seizure and coma. Healthcare professionals should inform patients about these risks and the signs and symptoms of morphine toxicity, and advise patients that if signs of toxicity are present, codeine should be stopped immediately and medical advice sought.

Estimates suggest that up to 10% of the Caucasian population may be poor metabolisers and up to 10% may be ultra-rapid metabolisers. The prevalence in Maori and Pacific people is not known.

Use in children

Children are more susceptible to the respiratory and circulatory depressant effects of opioid analgesics such as codeine. Parents and caregivers should be advised to seek medical advice immediately if signs of toxicity are present, such as excessive sleepiness, difficulty waking, difficulty breathing, confusion, slow heart rate or weak pulse. Paradoxical excitation or restlessness may also occur in paediatric patients receiving opioids (see section 4.9)

Use of codeine is contraindicated in:

- Children aged less than 12 years (see section 4.4)
- Adolescents aged less than 18 years for pain following surgery to remove tonsils or adenoids (see section 4.4)
- Adolescents aged less than 18 years in whom respiratory function might be compromised (see section 4.4)
- Adolescents aged less than 18 years for symptomatic relief of cough and cold (see section 4.4)

Use in the elderly

Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects, of these medications. Also geriatric patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment, and are therefore more likely to be adversely affected by opioid-induced urinary retention. The risk of constipation and faecal impaction is also greater in the elderly. Geriatric patients may metabolize or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually

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recommended for adults may be required, and are usually therapeutically effective for these patients.

4.5 Interaction with other medicines and other forms of interaction

The following interactions with codeine have been noted:

- Monoamine oxidase inhibitors – due to the possible risk of excitation or depression, avoid concomitant use and for 14 days after discontinuation of MAOI
- Alcohol – enhanced sedative and hypotensive effect, increased risk of respiratory depression
- Hypnotics and anxiolytics – enhanced sedative effect, increased risk of respiratory depression
- Anticholinergics – risk of severe constipation which may lead to paralytic ileus and/or urinary retention
- Metoclopramide and domperidone – antagonistic effect on GI activity
- Anti-diarrhoeal drugs – increased risk of severe constipation
- Anaesthetics – enhanced sedative and hypotensive effect
- Tricyclic antidepressants – enhanced sedative effect
- Antipsychotics, including phenothiazines – enhanced sedative and hypotensive effect
- Opioid antagonists – may precipitate withdrawal symptoms
- Quinidine – reduced analgesic effect
- Antihypertensive drugs – enhanced hypotensive effect
- Ciprofloxacin – avoid premedication with opioids as they reduce ciprofloxacin concentration
- Ritonavir – may increase plasma levels of opioid analgesics
- Mexiletine – delayed absorption of mexiletine
- Cimetidine – inhibits the metabolism of opioid analgesics causing increased plasma codeine concentrations

4.6 Fertility, pregnancy and lactation

Pregnancy

The risk-benefit balance must be carefully considered because opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high-dose use of Codeine prior to delivery may produce Codeine withdrawal symptoms in the neonate.

Although studies for teratogenic effects in humans have not been done, studies in animals have not shown codeine to cause adverse effects on foetal development.

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Studies in animals have shown codeine (single dose of 100mg per kg) to cause delayed ossification in mice and (in doses of 120mg per kg) increased resorption in rats.

The administration of opioid analgesics during labour may cause respiratory depression in the newborn infant. Withdrawal symptoms in new born infants have been reported with prolonged use of this class of drug.

Breast-feeding

Codeine is excreted into breast milk. However with usual analgesic doses, concentrations are generally low.

However, infants of nursing mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. When codeine enters the body and is metabolized, it changes to morphine. Nursing mothers taking codeine, who are ultra-rapid metabolisers of codeine, may have higher morphine levels in their breast milk. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies.

Use of codeine is contraindicated in women who are breastfeeding (see section 4.4)

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Codeine may cause drowsiness or a decrease in alertness in some patients. Patients should be cautioned about operating vehicles or machinery, or engaging in activities which require them to be fully alert.

4.8 Undesirable effects

In normal doses the commonest side effects of codeine and other opioid analgesics are nausea, vomiting, constipation (especially during chronic therapy), drowsiness and confusion.

The following have been noted:

Immune system disorders – rash, urticaria, pruritus, difficulty breathing, increased sweating, redness of flushed face, angioedema.

Nervous system disorders – confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucination, CNS excitation (restlessness/excitation), convulsions, mental depression, headache, nightmares, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia.

Eye disorders – miosis, blurred or double vision.

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Cardiac disorders – bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia.

Respiratory, thoracic and mediastinal disorders – respiratory depression.

Gastrointestinal Disorders – constipation, biliary spasm, nausea, vomiting, dry mouth.

Musculoskeletal, connective tissue and bone disorders – muscle rigidity.

Renal and urinary disorders – ureteral spasm, anti-diuretic effect, urinary retention.

Reproductive system and breast disorders – decrease in libido and potency.

Withdrawal effects – abrupt withdrawal precipitates a withdrawal syndrome.

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.

Tolerance diminished 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.

These effects occur more commonly in ambulant patients than in those at rest in bed.

Codeine has a lower dependence liability than other opioid agonists because of its comparatively lower potency with usual doses.

Withdrawal symptoms are also less severe than those produced by stronger opioid agonist analgesics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

Signs of overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, confusion, shallow breathing, and coma.

Signs of overdose in children include excessive sleepiness, difficulty waking, difficulty breathing, confusion, slow heart rate, weak pulse, paradoxical excitation or restlessness, and coma.

Toxic doses vary considerably with the individual and regular users may tolerate larger doses.

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Treatment

The stomach should be emptied by aspiration or lavage. A laxative may be given to aid peristalsis. Intensive supportive therapy may be required to correct respiratory failure and shocks. In addition, the specific antagonist naloxone hydrochloride is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses of opioid analgesics. A dose of 0.4mg to 2mg is given intravenously, intramuscularly or subcutaneously, repeated at intervals of 2 to 3 minutes if necessary, up to 10mg. The effect of naloxone may be of shorter duration than that of the opioid analgesic and additional doses may be required to prevent relapses.

The use of opioid antagonists such as naloxone, nalorphine and levallorphan in persons physically dependent on opioid agonists may induce withdrawal symptoms.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).}

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Codeine phosphate is an opioid analgesic with uses similar to those of morphine, but is much less potent as an analgesic and has only mild sedative effects. Its primary site of action is at the mu opioid receptors distributed throughout the central nervous system.

Codeine phosphate reduces intestinal motility through both a local and possibly central mechanism of action.

Codeine and its salts are absorbed from the gastro-intestinal tract and onset of analgesic action occurs 30 to 45 minutes after administration, when given orally.

Peak effect is reached within 1 to 2 hours and the duration of analgesic action is 4 hours.

5.2 Pharmacokinetic properties

Codeine is readily absorbed from the gastro-intestinal tract and metabolised by O- and N- demethylation in the liver to morphine and norcodeine which, with codeine, are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Most of the excretion products appear in the urine within 6 hours and 40 to 60 percent of the codeine is excreted free or conjugated, approximately 5 to 15 percent as free and conjugated morphine and about 10 to 20 percent free and conjugated norcodeine.

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.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For Codeine 15mg

Maize starch, Lactose, Magnesium stearate

For Codeine 30mg

Acacia Gum, Maize starch, Lactose, Talc Purified, Magnesium stearate

For Codeine 60mg

Maize starch, Lactose, Magnesium stearate

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months from date of manufacture when stored at 25°C

6.4 Special precautions for storage

Protect from light and moisture. Store at or below 25°C. Keep out of reach of children.

6.5 Nature and contents of container

Codeine 15mg Tablets: Bottle, glass. 100s & 500s

Codeine 30mg Tablets: Bottle, glass. 100s & 500s

Codeine 60mg Tablets: Bottle glass. 100s

Please note that not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug C2.

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8. SPONSOR

PSM Healthcare Limited, t/a API Consumer Brands
14-16 Norman Spencer Drive
PO Box 76 401
Manukau
AUCKLAND 2241
Telephone 0508 776746

9. DATE OF FIRST APPROVAL

30/12/1969

10. DATE OF REVISION OF THE TEXT

May 2018

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
All sections November 2017	Update to the SPC-style format only (required as part of any changes to the data sheet from 1 March 2017) and other minor changes.
May 2018	Contraindications added for: <ul style="list-style-type: none">• children aged less than 12 years for all indications• adolescents aged less than 18 years for pain following surgery to remove tonsils and adenoids• adolescents aged less than 18 years in whom respiratory function might be compromised• adolescents aged less than 18 years for cough and cold symptoms• breastfeeding mothers Sections 4.2, 4.3, 4.4 and 4.6 updated