AUSTRALIAN PRODUCT INFORMATION – GOLD CROSS CODEINE (CODEINE PHOSPHATE HEMIHYDRATE) LINCTUS

WARNINGS

Hazardous and harmful use
Gold Cross Codeine Linctus contains codeine and poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.4SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Life threatening respiratory depression
Serious, life-threatening or fatal respiratory depression may occur with the use of Gold Cross Codeine Linctus. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol
Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimuthem required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking Gold Cross Codeine Linctus.

1 NAME OF THE MEDICINE

Codeine phosphate hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate hemihydrate 5 mg/mL

Excipients with known effects: sucrose and methyl hydroxybenzoate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Gold Cross Codeine Linctus is a clear, almost colourless, oral liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Relief of unproductive, dry and intractable coughs associated with colds and flu.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults: 5 mL every four to six hours.

(See also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use.)

4.3 CONTRAINDICATIONS

Gold Cross Codeine Linctus is contraindicated for use in patients who are:

- CYP2D6 ultra-rapid metabolisers (see 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – CYP2D6 metabolism);
- younger than 12 years
- (see 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – Paediatric use);
- aged between 12-18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, due to an increased risk of developing serious and life-threatening adverse reactions (see 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – Paediatric use).
- Breastfeeding (see 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation).
- After operations on the biliary tract as codeine may cause biliary contraction.
- In the presence of acute alcohol intoxication, head injuries or conditions in which intracranial pressure is raised.
- Severe respiratory disease, acute respiratory disease and respiratory depression.
- in heart failure secondary to chronic lung disease.
- Codeine is contraindicated in patients taking MAOI's or within ten days of stopping such treatment.
- Due to codeine's structural similarity to morphine and oxycodone, patients who experience systemic allergic reactions (generalised rash, shortness of breath) to these drugs should not receive codeine.
- Codeine is contraindicated in patients with diarrhoea caused by poisoning, until the toxic substance has been eliminated from the gastrointestinal tract, or diarrhoea associated with pseudomembranous colitis caused by antibiotic administration, since codeine may slow the elimination of the toxic material or antibiotic.
- Gold Cross Codeine Linctus is contraindicated in patients with a history of allergic reactions to codeine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

Gold Cross Codeine Linctus contains the opioid codeine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Gold Cross Codeine Linctus at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed Gold Cross Codeine Linctus.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share Gold Cross Codeine Linctus with anyone else.

Respiratory depression
Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Gold Cross Codeine Linctus, but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with renal and hepatic impairment, and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 CONTRAINDICATIONS).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol
Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Gold Cross Codeine Linctus with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe Gold Cross Codeine Linctus concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking Gold Cross Codeine Linctus.

Tolerance, dependence and withdrawal
Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing Gold Cross Codeine Linctus in a person who may be physically dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually.

Accidental ingestion/exposure
Accidental ingestion or exposure of Gold Cross Codeine Linctus, especially by children, can result in a fatal overdose of codeine. Patients and their caregivers should be given information on safe storage and disposal of unused Gold Cross Codeine Linctus (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

Ceasing opioids
Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking and the physical and psychological attributes of the patient. During tapering, patients require regular review and support to manage any psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). If the patient is experiencing serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Identified precautions

- Codeine should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, or shock;
- Codeine should be administered with caution in patients with prostatic hypertrophy, urethral stricture or recent urinary tract surgery since codeine may cause urinary retention.

<u>CYP2D6 metabolism</u>

Gold Cross Codeine Linctus is contraindicated for use in patients who are CYP2D6 ultra-rapid metabolisers.

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. 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. Children are particularly susceptible due to their immature airway anatomy. Deaths have been reported in children with rapid metabolism who were given codeine

for analgesia post adenotonsillectomy. Morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of rapid metaboliser mothers who take codeine.

The prevalence of codeine ultra-rapid metabolism by CYP2D6 in children is not known, but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations. (See also the sections 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – Paediatric use and 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation).

Use in hepatic impairment

Codeine should be given with caution or in reduced doses to patients with impaired hepatic function.

Use in the elderly

Codeine should be used with caution in elderly or debilitated patients because of the danger of respiratory or cardiac depression.

The elderly are more likely to have age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

Paediatric use

Gold Cross Codeine Linctus is contraindicated for use in children:

• younger than 12 years.

• aged between 12-18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and /or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism (See 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – CYP2D6 metabolism).

Effects on laboratory tests

- Plasma amylase and lipase activity: Codeine may cause increased biliary tract pressure, thus increasing plasma amylase and/or lipase concentrations.
- Gastric emptying studies: Gastric emptying is delayed by codeine so gastric emptying studies will not be valid.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

- CNS depressants: Concomitant use of opioids and other CNS depressant medicines such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tranquillisers, general anaesthetics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, including alcohol, may potentiate the effects of CNS depressants and result in sedation, respiratory depression, coma and death (see also section 4.4 Special Warnings and Precautions for Use – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol).

- Antihistamines: Concomitant use of codeine and antihistamines with anticholinergic effects may result in an increased risk of severe constipation and/or urinary retention. Codeine may potentiate the CNS depressant effects of certain antihistamines.
- Monoamine Oxidase Inhibitors: Serious and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAO inhibitors or within 10 days of stopping such treatment. Caution is advised with the combination of codeine and selective MAO inhibitors (reversible inhibitors of Monoamine Oxidase A).
- Quinidine: Quinidine interferes with the metabolism of codeine to morphine lowering the analgesic effect of codeine.
- Cimetidine: Cimetidine may reduce the metabolism of codeine, enhancing the possibility of codeine toxicity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No significant effects have been reported.

Use in pregnancy – Pregnancy Category A

Opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate.

Use in lactation.

Gold Cross Codeine Linctus is contraindicated during breast-feeding (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - CYP2D6 metabolism) due to risk of respiratory depression in the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breast-feeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Codeine is excreted into human breast milk. Codeine is partially metabolised by cytochrome P450 2D6 (CYPD26) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breastfed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses (See 4.4 SPECIAL WARNINGS & PRECAUTIONS FOR USE – CYP2D6 metabolism).

Therefore, Gold Cross Codeine Linctus is contraindicated for use during breastfeeding. However, in circumstances where a breastfeeding mother requires codeine therapy, breastfeeding should be suspended, and alternative arrangements should be made for feeding the infant for any period during codeine treatment.

Breastfeeding mothers should be told how to recognise signs of high morphine levels in themselves and their babies. For example, in a mother, symptoms include extreme sleepiness and trouble caring for the baby. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Medical advice should be sought immediately.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned that codeine may cause sedation and impair their ability to perform activities requiringmental alertness or physical coordination (e.g. operating machinery, driving a motor vehicle). Alcohol should be avoided.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

- **Gastrointestinal:** Common: constipation. Uncommon: nausea, vomiting, dry mouth
- **Neurological:** Common: dizziness, drowsiness. Uncommon: euphoria, dysphoria, nervousness, restlessness, paradoxical CNS stimulation (especially in children), confusion, headache, blurred or double vision
- **Hypersensitive:** Uncommon: skin rashes and other allergic reactions (pruritus, urticaria), histamine release (hypotension, sweating, flushing of the face, tachycardia, breathlessness)
- **Genitourinary:** Uncommon: urinary retention or hesitance
- **Withdrawal syndrome:** a withdrawal syndrome may be precipitated when chronic administration of codeine is discontinued, or opioid antagonists administered. The following symptoms may be observed: body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors, shivering, stomach cramps, nausea, sleep disturbance, increased sweating and yawning, weakness, tachycardia, fever, irritability, vomiting, mydriasis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms of codeine overdosage include vomiting, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis, miosis and coma.

Treatment of overdose involves the following measures:

Support respiratory and cardiovascular function. Assisted ventilation may be necessary.

Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

If clinically significant respiratory or cardiac depression is present, give naloxone. The usual adult dose is 0.4 - 2.0 mg intravenously (or subcutaneously), repeated every 2 to 3 minutes if necessary. The use of naloxone in physically dependent patients may precipitate withdrawal symptoms.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Codeine causes suppression of the cough reflex by a direct effect on the cough centre in the medulla of the brain and appears to exert a drying effect on the respiratory tract mucosa and to increase viscosity of bronchial secretions.

On a weight basis, antitussive activity of codeine is less than that of morphine. Codeine also has mild analgesic and sedative effects.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Codeine is well absorbed after administration by mouth. It is metabolised in the liver to morphine and norcodeine, which with codeine are excreted in the urine, partly as conjugates with glucuronic acid. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite. Most of the excretion products appear in the urine within 6 hours and excretion of up to 86% of the dose is almost complete in 24 hours. About 70% of the codeine is excreted free or conjugated, about 10% as free and conjugated morphine, and about 10% as free and conjugated norcodeine. Only traces are excreted in the faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No significant effects have been reported.

Carcinogenicity

No significant effects have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene glycol, sucrose, glycerol, methyl hydroxybenzoate, and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass (Type III coloured) bottle, linctus containing codeine phosphate hemihydrate 5 mg/mL, 100 mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Codeine phosphate hemihydrate is a small, colourless, odourless crystal or a white, odourless crystalline powder. Codeine phosphate hemihydrate is soluble in 4 parts of water, slightly soluble in ethanol (96%), practically insoluble in chloroform and ether.

Chemical structure

Codeine phosphate hemihydrate is (5R,6S)-7,8-didehydro-4,5-epoxy-3-methoxy-N-methylmorphinan-6-ol dihydrogen orthophosphate hemihydrate.

The molecular formula is C18H21NO3,H3PO4,½H2O. The molecular weight is 406.4.

CAS number

CAS - 41444-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug - Schedule 8

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited
Level 10, 12 Help St
Chatswood NSW 2067
Phone (Toll Free): 1800 630 056

9 DATE OF FIRST APPROVAL

11 November 1991

10 DATE OF REVISION

16 July 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
ALL	PI Reformat
Boxed warning	Addition of boxed warning

4.3 Contraindications	Removed contraindication for respiratory depression
4.4 Special warnings & precautions for use	Added warnings on respiratory depression, addiction, tolerance and dependency, accidental ingestion, and cessation.