AUSTRALIAN PRODUCT INFORMATION –

RIKODEINE® (DIHYDROCODEINE TARTRATE AND SORBITOL) ORAL LIQUID

WARNINGS

Hazardous and harmful use

Rikodeine Oral Liquid contains dihydrocodeine 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 4.4. Special Warnings and Precautions for Use*).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of Rikodeine Oral Liquid. 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 minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking Rikodeine Oral Liquid.

1 NAME OF THE MEDICINE

Dihydrocodeine tartrate and Sorbitol.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL of Rikodeine Oral Liquid contains dihydrocodeine tartrate 19 mg, and sorbitol 4.4 g. It also contains sucrose, citric acid, methyl hydroxybenzoate, amaranth, strawberry flavour 73858 and water.

Excipients with known effects: sugars, hydroxybenzoates, sorbitol (26.4 g per 60 mL (maximum recommended daily dose).

3 PHARMACEUTICAL FORM

Oral liquid-– pink coloured solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For relief of stubborn, unproductive cough.

4.2 DOSE AND METHOD OF ADMINISTRATION

Age	Dosage	How Often
Adults and Children 12 years and over	5 to 10 mL	Every 4-6 hours as required
Children between 6-11 years Use in children ages 6-11 years only on the advice of a doctor, pharmacist or nurse practitioner	2.5 to 5 mL	
Do not use in children aged less than 6 years		

Initial dosage should be reduced in the elderly as there may be a marked variability in pharmacokinetics in the elderly (See *Metabolism and Excretion in section 5.2 Pharmacokinetic Properties*).

4.3 CONTRAINDICATIONS

1. Hypersensitivity to dihydrocodeine, other opioids, or other components listed
2. Opioid derivatives such as dihydrocodeine are generally but not always contraindicated in the following disorders: acute alcoholism, convulsive disorders, paralytic ileus, head injuries andconditions in which the intracranial pressure is raised. It should not be given to a comatose patient
3. Severe respiratory disease, acute respiratory disease and respiratory depression.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

Rikodeine Oral Liquid contains the opioid dihydrocodeine tartrate and is a potential drug of abuse, misuseand addiction. Addiction can occur in patients appropriately prescribed Rikodeine Oral Liquid at recommended doses. Abuse of dihydrocodeine has been reported.

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 Rikodeine Oral Liquid.

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 Rikodeine Oral Liquid 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 Rikodeine Oral Liquid 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 Rikodeine Oral Liquid 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 Rikodeine Oral Liquid 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 Rikodeine Oral Liquid.

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 Rikodeine Oral Liquid 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 Rikodeine Oral Liquid, especially by children, can result in a fatal overdose of dihydrocodeine tartrate. Patients and their caregivers should be given information on safe storage and disposal of unused Rikodeine Oral Liquid (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.

Lung

As dihydrocodeine may cause the release of histamine, it should be given with caution in asthmatics, in patients with decreased respiratory reserve (eg. emphysema), cor pulmonale or chronic obstructive respiratory disease (see *section 4.4 Special Warnings and Precautions for Use – Respiratory depression)*.

Gastrointestinal

Opioids should be given with caution or in reduced doses to patients with inflammatory or obstructive bowel disorders, biliary tract disorders or inflammation of the pancreas. Rikodeine Oral Liquid contains 26.4 g sorbitol in 60 mL (maximum daily dose), which may have a laxative effect or cause diarrhoea in some people.

Others

Dosage of dihydrocodeine should be reduced in hypothyroidism. Opioids should be given with caution or in reduced doses to patients with adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, or myasthenia gravis.

Use in hepatic impairment

Dosage of dihydrocodeine should be reduced in chronic hepatic disease.

Use in renal impairment

Caution is advised in patients with severe renal impairment as dose accumulation may occur. In the elderly with lower renal clearance, there is marked variability in the pharmacokinetics so small doses may be needed initially (See *Metabolism and Excretion in section 5.2 Pharmacokinetic Properties*).

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Rikodeine Oral Liquid may enhance the effects of CNS depressants and may result in sedation, respiratory depression, coma and death. Examples of CNS depressants include other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tranquillisers, tricyclic antidepressants, antipsychotics, centrally-active anti-emetics, antihistamines and other CNS depressants, including alcohol (see *Section 4.4 Special Warnings and Precautions for Use – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol*).

Quinidine: Two studies (n = 4 and n = 10) and biochemical evidence suggest that the analgesic effects of dihydrocodeine may be reduced or lost if quinidine is administered concurrently in extensive metabolisers (CYP2D6) of codeine. This is the majority of the population. Poor metabolisers of codeine will not be affected. About 6 to 10 % of Caucasians lack this enzyme. The incidence of lack of this enzyme is lower in South-East Asians.

The possibility of interactions between dihydrocodeine and other drugs which can inhibit the enzyme CYP2D6, such as phenothiazines and antipsychotic agents should be considered.

Consideration should also be given to potential interactions with other medications, which occur with other opioids:

- Medications with anticholinergic effects such as antihistamines with anticholinergic effects, or tricyclic antidepressants, which may increase constipation and/or urinary retention;
- Antihypertensive medications (possible additive hypotensive effects);
- Antiperistaltic antidiarrhoeals (may increase risk of severe constipation);
- Monoamine oxidase (MAO) inhibitors (may lead to anxiety, confusion, severe respiratory depression);
- Neuromuscular blockers (may lead to additive respiratory depressant effects);
- Opioid agonists (eg. codeine, morphine, pethidine, etc) may increase the toxic effects of dihydrocodeine;
- Opioid antagonists (eg naloxone).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category A

Medicines have been taken by large numbers of pregnant women and women of child-bearing age for many years without proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. As with all medicines the associated risk to the foetus should be considered against the anticipated benefit to the mother.

Prolonged consumption late in pregnancy may risk causing respiratory depression and withdrawal symptoms in the neonate.

Use in lactation

No information is available. Rikodeine Oral Liquid should not be used in lactation unless the benefits outweigh the possible risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dihydrocodeine may cause sedation and may impair the ability of the patient to drive or operate machinery. Patients treated withdihydrocodeine should be cautioned that their ability might be reduced.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

More common reactions

Constipation, although recorded, is less common than with codeine. Drowsiness, nausea, vomiting, headache, respiratory depression and vertigo may occur.

In 12 healthy volunteers, opiate-related side effects occurred especially with higher steady-state doses: headache, nausea, vomiting, dizziness, constipation, stomach pain, mild urinary retention, dry mouth and mild euphoria. The side effects were mild and reversible, and none of the subjects had to discontinue the study.

In another randomised, placebo controlled, blinded, cross-over study of healthy volunteers (n=100, 95 completed trial), a significant incidence of nausea and dizziness was observed with dihydrocodeine, but other side effects were not significantly different (p=0.05) to the level after administration with placebo.

In a randomised, placebo controlled, double-blind, cross-over study of 18 patients with chronic obstructive airways disease, there were no significant differences in peak flow, drowsiness, nausea, constipation or anxiety.

Less common reactions

Other adverse effects have been infrequently reported include central nervous system effects such as dizziness, visual disturbances and hallucinations, cardiovascular effects such as atrial fibrillation, circulatory failure and syncope and dermal effects such as pruritus, rash and urticaria.

Rikodeine contains sorbitol, which may have a laxative effect or cause diarrhoea in some people..

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

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

Symptoms and signs

The blood levels of dihydrocodeine found in impaired individuals and in fatalities show a wide overlap in ranges. In three fatal cases the amount of parent drug always exceeded dihydrocodeine-glucuronide formation and dihydromorphine concentrations ranged from 0.16 to 0.21 mg/mL. Dihydrocodeine overdose is characterised by pinpoint pupils, respiratory depression (reduced respiratory rate and/or tidal volume, Cheynes-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin and sometimes hypotension and bradycardia. Overdose has been associated with evidence of acute renal failure and hepatic impairment. Continued overdosage may result in apnoea, circulatory collapse, cardiac arrest and death.

Treatment

Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway, supplemental oxygen and controlled or assisted ventilation with maintenance of the fluid balance. The narcotic antagonist, naloxone hydrochloride, is a specific antidote and an appropriate dose should be administered as necessary, in accordance with the patient's response.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Cough suppressant with analgesic properties.

Dihydrocodeine is a semi-synthetic opioid, which is frequently used as an analgesic and antitussive / cough suppressant drug. It is formulated in Rikodeine Oral Liquid as an antitussive. As an antitussive, the recommended dose for dihydrocodeine tartrate is lower than the usual recommended dose for analgesia. The antitussive effects of dihydrocodeine are mediated through direct action on receptors in the cough centre of the medulla.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of dihydrocodeine tartrate 30 mg and 60 mg to seven healthy volunteers, the serum concentration-time curves indicated a rapid absorption of dihydrocodeine with mean peak serum concentrations were achieved at 1.6 to 1.8 hours. The rate of absorption was independent of administered dose. The mean half-lives varied between 3.3 to 4.5 h. The mean bioavailability of orally administered dihydrocodeine was 21 % (range 12-34 %). After intravenous administration of 30 mg dihydrocodeine tartrate (n=7 healthy volunteers), the peak serum levels were significantly greater (over 8 times higher) than those achieved after oral dosing (30 mg or 60 mg). The peak serum levels of the acidic metabolites (dihydromorphine and dihydrocodeine glucuronide) occurred between 1.8h to 2.0h after oral administration and 2.2 to 2.5h after intravenous administration and were significantly higher after oral administration. The low oral bioavailability of dihydrocodeine, together with the earlier and higher plasma levels of the acid metabolites after oral dosing compared to IV dosing, is suggestive of substantial first-pass metabolism.

In the dose range 60 to 120 mg as single and multiple doses the pharmacokinetics of dihydrocodeine and its active metabolite dihydromorphine are linear.

Pharmacokinetics in Elderly: The effect of age on the pharmacokinetics of dihydrocodeine was investigated in 8 elderly (74 to 90 years) patients and 8 young (21 to 29 years) volunteers. After multiple oral dosing of dihydrocodeine 30 mg four times a day for 3 days, the maximum plasma concentration of dihydrocodeine was significantly higher in the elderly (199 $\pm$ 155 ng/m) than in the young (174 $\pm$ 53 ng/mL); and the area under the plasma concentration-time curve in the elderly was approximately 25 % higher than in the young which was considered to be likely to be clinically significant. The greater plasma concentrations in the elderly compared to the young was more likely due to a decrease in first pass effect in the elderly patients. Results from this study suggest that the recommended doses in the elderly may need to be reduced.

Pharmacokinetics in Chronic Renal Failure Patients: The pharmacokinetics of a single 60 mg oral dose of dihydrocodeine were studied in 9 patients with chronic renal failure treated by haemodialysis and 9 subjects with normal renal function. In patients with chronic renal failure, the mean peak plasma dihydrocodeine concentration occurred later and the area under the plasma concentration-time curve was greater than in the normal subjects. Furthermore, the drug was still detectable after 24 hours in all the patients with renal failure but was only detectable in only three of the normal subjects. Possible explanations for these findings include differences in absorption, the volume of distribution, the rate of metabolism, and the rate of excretion of the drug.

Metabolism & Excretion

The metabolism of dihydrocodeine includes O-demethylation to dihydromorphine; N-demethylation to nordihydromorphine; and conjugation of parent drug and hydroxylated metabolites with glucuronic acid.

The cytochrome P450-2D6 (CYP2D6) is the major enzyme mediating O-demethylation of dihydrocodeine to dihydromorphine. In contrast, nordihydrocodeine formation is predominantly catalysed by cytochrome P450-3A (CYP3A).

The pharmacokinetics of dihydrocodeine was studied in subjects with differing rates of metabolism via the enzyme CYP2D6, in six extensive (metabolic ratio < 1), two intermediate (1<MR<20) and six poor metabolisers (MR ≥ 20) of sparteine / debrisoquin, were compared following administration of a single oral dose of dihydrocodeine. Results from this study showed that there were no significant differences in the pharmacokinetics of dihydrocodeine between extensive and poor metabolisers in maximum serum concentration, area under the curve and terminal half-life. However, the area under the serum concentration versus time curve and total urinary recovery of dihydromorphine were significantly lower in poor metabolisers compared with extensive metabolisers. No significant differences between extensive and poor metabolisers were detected in urine for conjugated dihydrocodeine (approximately 30 %), unconjugated dihydrocodeine (approximately 31 %), conjugated nordihydrocodeine (5-6 %) or unconjugated nordihydrocodeine (16-20 %). In conclusion, this study demonstrated that following oral administration, dihydrocodeine is mainly excreted in urine as the parent compound or its conjugates in extensive and poor metabolisers. The O-demethylation of dihydrocodeine to dihydromorphine (mainly by CYP2D6) is impaired in poor metabolisers: the dihydromorphine metabolite, only accounts for 0.4-2.8 % of the dose in the poor CYP2D6 metabolisers and 3.5-17.1 % in the extensive CYP2D6 metabolisers. Consideration should be given to the possibility that patients who metabolise drugs poorly via CYP2D6 may obtain reduced benefit from dihydrocodeine due to reduced formation of an active metabolite, dihydromorphine.

In healthy adult males, CYP2D6 extensive metabolisers (n=12), the pharmacokinetics of dihydrocodeine and its active metabolite dihydromorphine following multiple oral dosing of 60-120 mg dihydrocodeine are shown to be linear.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine (See also *Section 4.5 Interactions with Other Medicines and Other Forms of Interactions*).

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Amber PET bottle, 30 mL*, 100 mL, 200 mL

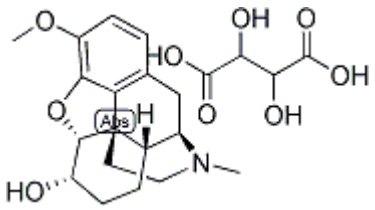
* Not currently marketed

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

Dihydrocodeine tartrate



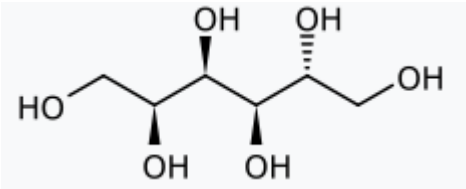
Dihydrocodeine tartrate is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol hydrogen tartrate.

It is odourless or almost odourless colourless crystals or a white crystalline powder. It is freely soluble in water and is sparingly soluble in alcohol.

Molecular formula: $C_{22}H_{29}NO_9$

CAS number: 5965-13-9

Sorbitol



Molecular formula: $C_6H_{14}O_6$

CAS number: 50-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S3) Pharmacist Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited

Level 10, 12 Help Street

Chatswood NSW 2067

Australia

Toll free: 1800 630 056

9 DATE OF FIRST APPROVAL

4 July 1991

10 DATE OF REVISION

24 August 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Box warning 4.3 4.4 4.5	Safety-related request to: • Include boxed warning ; • Add new Contraindication for severe and acute respiratory disease andrespiratory depression; • Add new Precautions for Hazardous & harmful use; Respiratory depression;Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol,; Tolerance, dependence and withdrawal; Accidental ingestion/exposure; Ceasing opioids; • Add new effects when used with CNS depressants & examples of CNS depressants following the Opioid reforms process as requested by the Signal InvestigationUnit of the Pharmacovigilance and Special Access Branch