PRODUCT INFORMATION

RIKODEINE™ Oral Liquid

Product Name:
Rikodeine Oral Liquid

Product Description
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. Each 10mL of Rikodeine Oral Liquid contains dihydrocodeine tartrate 19mg, and sorbitol 4.4g in a clear, red, strawberry flavoured liquid. It also contains sucrose, citric acid anhydrous, methyl hydroxybenzoate, amaranth Cl16185 and water. Rikodeine Oral Liquid does not contain alcohol, lactose or gluten.

Pharmacology
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.

Pharmacokinetics

Absorption: Following oral administration of dihydrocodeine tartrate 30mg and 60mg 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 30mg dihydrocodeine tartrate (n=7 healthy volunteers), the peak serum levels were significantly greater (over 8 times higher) than those achieved after oral dosing (30mg or 60mg). 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 120mg as single and multiple doses the pharmacokinetics of dihydrocodeine and its active metabolite dihydromorphine are linear.

Metabolism and 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 \( \leq 1 \)), two intermediate \( (1<MR<20) \) and six poor metabolisers \( (MR \geq 20) \) 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 60-120mg dihydrocodeine are shown to be 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 30mg four times a day for 3 days, the maximum plasma concentration of dihydrocodeine was significantly higher in the elderly \( (199 \pm 155 \text{ ng/m}) \) than in the young \( (174 \pm 53 \text{ ng/mL}) \); 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 60mg 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.
Indications
For relief of stubborn, unproductive cough.

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 asthma attack, respiratory depression, acute alcoholism, convulsive disorders, paralytic ileus, head injuries and conditions in which the intracranial pressure is raised. It should not be given to a comatose patient.

Precautions
CNS: Dihydrocodeine (like other opioids) may cause CNS depression, it should be given with caution to patients with CNS depression.

Dihydrocodeine may impair the ability of the patient to drive or operate machinery.

Patients treated with dihydrocodeine should be cautioned that their ability might be reduced.

Renal: 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 Pharmacokinetics-Metabolism and excretion.

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.

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

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

As with many other opiates, abuse of dihydrocodeine has been reported.

Use in 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 should not be used in lactation unless the benefits outweigh the possible risk to the infant.

Interactions with other drugs

Rikodeine Oral Liquid may enhance the effects of CNS depressants. These include alcohol, and medications such as antiemetics, antihistamines, hypnotics and sedatives, and tranquillisers.

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).

Interference with clinical, laboratory and other tests:

No information is available.

Adverse Reactions

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.

Dosage and Administration

Adults: 5 to 10 mL every four to six hours
Children: 6 to 12 years 2.5 to 5 mL every four to six hours
4 to 5 years 2.0 to 2.5 mL every four to six hours

Not recommended for children under 4 years.

Initial dosage should be reduced in the elderly as there may be a marked variability in pharmacokinetics in the elderly. See Pharmacokinetics -Metabolism and excretion..

Overdosage

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 0.21mg/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.

Storage

Store below 30°C
Presentation
100mL, 200mL

Poisons Schedule
S3 Pharmacist Only

Manufacturer
iNova Pharmaceuticals (Australia) Pty Ltd
9-15 Chilvers Road
Thornleigh NSW 2120

TGA approval
13 January 2004.

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