

AUSTRALIAN PRODUCT INFORMATION
CIZINATE® (CINNARIZINE/DIMENHYDRINATE) 20 MG/40 MG TABLET

1 NAME OF THE MEDICINE

Cinnarizine

Dimenhydrinate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CIZINATE tablets contain the active ingredients cinnarizine and dimenhydrinate.

Each CIZINATE 20 mg/40 mg tablet contains 20 mg of cinnarizine and 40 mg of dimenhydrinate.

Cinnarizine is a white to almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, soluble in acetone and slightly soluble in ethanol and methanol.

Dimenhydrinate, the chlorotheophylline salt of diphenhydramine, is a white to almost white, crystalline powder or colourless crystals. It is slightly soluble in water and freely soluble in ethanol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

CIZINATE 20 mg/40 mg tablets are a white to almost white, round, biconvex uncoated tablet 8 mm in diameter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term, symptomatic treatment of vertigo of various causes, in adults who have not responded to alternative treatments.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

The recommended dose for adults is one tablet three times daily. The lowest dose for the shortest duration to achieve symptom control should be used. The recommended dose should not be exceeded.

CIZINATE tablets should be swallowed without chewing with some liquid after meals to minimise any gastric irritation.

In general, the duration of treatment should not exceed four weeks. Patients should undergo a reassessment of the risk/benefit if treatment beyond 4 weeks is contemplated.

Elderly

No dose adjustment is necessary.

Renal impairment

CIZINATE is contraindicat

Patients should be advised to cease treatment with [tradenam] immediately and seek medical advice if any abnormal movements such as, shaking, twitching or twisting movements, muscle stiffness, restless legs, stiff posture, slowed shuffling walk or a need to be in constant motion arise.

CIZINATE should not be given to patients with pre-existing extrapyramidal movement disorders such as Parkinson's disease.

Use with caution in the following circumstances:

Cinnarizine/dimenhydrinate does not reduce blood pressure significantly; however, it should be used with caution in hypotensive patients.

Cinnarizine/dimenhydrinate tablets should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy, e.g. raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism or severe coronary heart disease.

Use in hepatic impairment

CIZINATE is contraindicated in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

No studies in patients with hepatic impairment are available.

Both cinnarizine and dimenhydrinate are extensively metabolised by hepatic cytochrome P450 enzymes. The plasma concentrations of the unchanged drugs and their half-lives will increase in patients with severe hepatic impairment. This has been shown for diphenhydramine in patients with cirrhosis.

Use in renal impairment

renal impairment) (see Section 4.3 CONTRAINDICATIONS). mL/min (severe

Diphenhydramine is completely excreted renally, and patients with severe renal impairment were excluded from the clinical development programme.

Use in the elderly

Safety and efficacy trials conducted with FDC included patients up to 83 years of age, however no relevant sub-analyses were performed in patients aged over 65 years.

Increased age may be a potential risk factor associated with cinnarizine induced extrapyramidal adverse events.

Paediatric use

The safety and efficacy of CIZINATE in children and adolescents under the age of 18 years has not been established. No data is available. CIZINATE should not be given to children or adolescents aged less than 18 years.

Effect on laboratory tests

Interactions with laboratory tests have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Information relevant to potential interactions between cinnarizine and diphenhydramine and other medicinal products is limited.

studies in human microsomal fractions and other animal studies demonstrate that cinnarizine metabolism is mediated by CYP2D6, CYP2B6, CYP2C9 and CYP1A2, with CYP2D6 the predominant pathway.

As CYP2D6 is prominently involved in the metabolism of both diphenhydrinate and cinnarizine, and diphenhydramine is known to inhibit CYP2D6 mediated metabolism.

Accordingly, care should be taken when administering the combination product with CYP2D6 substrates such as tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics, beta blockers and antiarrhythmics.

The anticholinergic and sedative effects of cinnarizine/dimenhydrinate may be potentiated by monoamine oxidase inhibitors. Procarbazine may enhance the effect of cinnarizine/dimenhydrinate tablets.

In common with other antihistamines, cinnarizine/dimenhydrinate tablets may potentiate the sedative effects of CNS depressants including alcohol, barbiturates, narcotic analgesics and tranquillisers. Patients should be advised to avoid alcoholic drinks. Cinnarizine/dimenhydrinate tablets may also enhance the effects of anti-hypertensives, ephedrine and anticholinergics such as atropine and tricyclic antidepressants.

Cinnarizine/dimenhydrinate tablets may mask ototoxic symptoms associated with aminoglycosidic antibiotics and mask the response of the skin to allergic skin tests.

The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class Ia and Class III anti-arrhythmics) should be avoided.

Cinnarizine may oppose the effect of betahistine. CIZINATE should not be administered with betahistine.

Dimenhydrinate contains a caffeine derivative (8-chlorotheophylline). Caffeine is metabolised by the cytochrome P450 1A2 enzyme, and therefore it is possible that 8-chlorotheophylline may inhibit or potentiate the response of common medications such as diltiazem, verapamil, olanzapine, oral contraceptives and omeprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of cinnarizine and dimenhydrinate on fertility are not known.

Use in pregnancy

Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

At high doses associated with maternal toxicity in rats, cinnarizine decreased litter size, increased the number of resorbed foetuses and decreased the birth weight of pups. The teratogenic risk of the single actives dimenhydrinate/diphenhydramine and cinnarizine is low. No teratogenic effects were observed in animal studies.

When administered to pregnant guinea pigs, cinnarizine was recovered from the foetus. The proportion of administered dose recovered from the foetus, compared to the dam, was generally less than 25%.

There are no data from the use of cinnarizine/dimenhydrinate tablets in pregnant women.

Based on human experience dimenhydrinate is suspected to have an oxytocic effect and may shorten labour.

Cinnarizine/dimenhydrinate tablets are not recommended during pregnancy.

Use in lactation

Cinnarizine and dimenhydrinate are excreted in human breast milk. Cinnarizine/dimenhydrinate tablets should not be used during breastfeeding

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cinnarizine/dimenhydrinate tablets may have minor influence on the ability to drive and use machines.

Cinnarizine/dimenhydrinate tablets may cause drowsiness, especially at the start of treatment. Patients affected in this way should not drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequently reported adverse drug reactions (ADR) in patients taking FDC in clinical trials are somnolence (including drowsiness, tiredness, fatigue, daze), dry mouth and headache. These reactions are usually mild and disappear within a few days even if treatment is continued. The overall frequency of ADRs associated with CIZINATE in all clinical trials and following spontaneous reports are included in the next table.

Table 1: Tabulated list of adverse reactions

Frequency of ADR	Common	Uncommon	Rare	Very rare <1/10,000
Body system:				
Blood and lymphatic system disorders				Leucopenia Thrombopenia Aplastic anaemia
Immune system disorders			Hypersensitivity reactions (e.g. cutaneous reactions)	
Nervous system disorders	Somnolence Headache	Paraesthesia Amnesia Tinnitus Tremor Nervousness Convulsions		
Eye disorders			Visual disorders	
Gastrointestinal disorders	Dry mouth Abdominal pain	Dyspepsia Nausea Diarrhoea		
Skin and subcutaneous tissue disorders		Perspiration Rash	Photosensitivity	
Renal and urinary disorders			Urinary hesitancy	

In addition the following adverse reactions are associated with cinnarizine and dimenhydrinate (frequency cannot be estimated from the available data):

Dimenhydrinate:

paradoxical excitability (especially in children),
worsening of an existing angle - closure glaucoma,
reversible agranulocytosis.

Cinnarizine:

constipation,
weight gain,
tightness of the chest,
cholestatic jaundice,
extrapyramidal symptoms,
lupus-like skin reactions,
lichen planus.

Reporting suspected adverse reactions

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 <http://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

Symptoms of overdose with CIZINATE include drowsiness, dizziness and ataxia with anticholinergic effects such as dry mouth, flushing of the face, dilated pupils, tachycardia, pyrexia, headache and urinary retention. Convulsions, hallucinations, excitement, respiratory depression, hypertension, tremor and coma may occur, particularly in cases of ingestion of larger doses.

Management

In case of overdose treatment should be supportive and symptomatic

General supportive measures should be used to treat respiratory insufficiency or circulatory failure. Body temperature should be closely monitored, since pyrexia may occur as a consequence of antihistamine intoxication, especially in children.

Cramp-like symptoms may be controlled by careful application of a short-acting barbiturate. In cases of marked central-anticholinergic effects, physostigmine (after physostigmine test) should be administered slowly intravenously (or, if necessary, intramuscularly): 0.03 mg/kg body weight (adults max. 2 mg, children max. 0.5 mg).

Dimenhydrinate is dialyzable, however treatment of overdose by this measure is considered as unsatisfactory. Sufficient elimination can be achieved by means of haemoperfusion using activated charcoal.

No data are available concerning the dialysability of cinnarizine.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

studies have demonstrated that both diphenhydramine and cinnarizine have inhibitory activity at multiple molecular targets. Diphenhydramine is a potent inhibitor of histamine H₁ receptors and muscarinic acetylcholine receptors, whilst cinnarizine is a potent inhibitor of histamine H₁ and H₄ receptors and dopamine D₂ receptors and a less potent inhibitor of pressure-sensitive potassium channels and serotonin 2 receptors. All the aforementioned proteins are known to have functions in the central and/or peripheral vestibular system.

The rationale for combining both compounds into a fixed dose combination tablet is to provide a product with a dual mechanism of action, with cinnarizine primarily acting peripherally on the labyrinth, and dimenhydrinate acting predominately centrally on the vestibular nuclei and related vegetative centres in the brainstem. This product may then be useful in treating vertigo of various origins.

Clinical trials

The safety and efficacy of the fixed dose combination tablet (FDC) containing cinnarizine 20 mg and dimenhydrinate 40 mg is supported by five publications summarising the outcome of 9 well designed, randomised, controlled clinical trials (RCT). All RCT used a three times daily dosing regimen for FDC.

Four of the 9 RCT compared the efficacy of the FDC to equi-doses of the individual component medicines, while 3 studies compared the FDC to doses of the component monotherapies which were 2.5 times greater (cinnarizine 50 mg and dimenhydrinate 100 mg respectively) than the amount included in the FDC. Two of the RCT also included a placebo arm. The remaining study compared the FDC to betahistine 12 mg three times daily.

The FDC used in all trials contain the same quantities of cinnarizine and dimenhydrinate as the Australian formulation. The studies were performed in a total of 1235 adult patients with an average age in the early 50's. More females than males were included in the studies, with most individual RCT recruiting more than 60% females. All but one of the RCT recruited patients with vertigo of central, peripheral or combined central and peripheral origin. The remaining study recruited patients with vertigo due to unilateral vestibular failure or neuropathy.

The pivotal studies supporting the efficacy of FDC were reported as publications by Hahn 2001 and Pytel 2007.

Hahn 2006 was a multicentre, double blind, randomised, three arm, parallel-group, trial comparing the tolerability and efficacy of a FDC medicine containing 20mg of cinnarizine and 40mg of dimenhydrinate, to monotherapy with either 20mg cinnarizine or 40mg dimenhydrinate, in adult patients with vertigo of central, peripheral or mixed origin.

The objective of the study was to compare the efficacy and safety of FDC compared to the monocomponents in patients presenting to clinical practice with any symptom of vertigo, regardless of origin, and to test whether the efficacy of the FDC exceeds that of single components without increasing the incidence of adverse events.

The primary efficacy variable was the change in mean vertigo score (MVS) at week 4. The MVS was calculated by adding the individual scores recorded for each of the 12 vertigo symptoms by patients using a 5 point VAS (0=not present, 4=very strong), divided by 12. Secondary efficacy endpoints were the change in severity of vegetative symptoms associated with vertigo using the same VAS and the Unterberger and Romberg lateral and angular deviation tests, and nystagmus frequency in the caloric test. All assessments were performed at baseline, after one week of treatment and at 4 weeks.

The incidence, severity and relationship to study medicine of all observed or reported adverse events were recorded. The overall tolerability of treatments was assessed by both the participant and investigator at week 1 and 4 using a 4 point scale (poor to very good).

The change in MVS following the 4 week treatment period is shown in following table. Patients assigned FDC treatment demonstrated the greatest improvement in vertigo score during the 4 week study. At week 4 the MVS had decreased by > 80% in the FDC group compared to around 60% in the cinnarizine or dimenhydrinate groups. The differences in efficacy were significantly ($P < 0.001$) at both week 1 and 4.

Table 2: Change in MVS, point estimates and 95% CI of treatment differences and effect size.

Parameter	FDC (n=59)	Cinnarizine 20mg	Dimenhydrinate 40mg
Baseline MVS (mean±SD)	1.77±0.44	1.69±0.44	1.81±0.48
Week 1 MVS (mean±SD)	-0.73±0.44	-0.47±0.37*	-0.44±0.40*
(mean±SD)	-1.44±0.56	-1.04±0.53*	-1.06±0.56*
@ (mean, 95% CI)		0.35 (0.18, 0.52)	0.41 (0.24, 0.57)
Week 4 Cohens std diff (d, 95% CI)		0.74 (0.37, 1.12)	0.69 (0.31, 1.06)

@ comparator versus FDC * p < 0.001

Furthermore, 11 of the 59 participants treated with FDC were completely symptom free (defined as a MVS = 0) after 4 weeks of treatment, compared to none of the 60 participants treated with cinnarizine (difference p < 0.001) and one of 58 treated with dimenhydrinate (difference p < 0.01).

Cinnarizine was significantly less effective in reducing vegetative symptoms compared to FDC or dimenhydrinate at week 4. Significantly greater improvements in lateral sway were observed at 1 week but not week 4 in the FDC group compared to the other treatments.

Pytel 2007 was a multicentre, double blind, randomised, four arm, parallel-group, trial comparing the tolerability and efficacy of a FDC medicine containing 20mg of cinnarizine and 40 mg of dimenhydrinate to monotherapy with 50mg cinnarizine or 100mg dimenhydrinate, or placebo, in adult patients with vertigo of central, peripheral or mixed origin.

The objective of the study was to compare the efficacy and safety of FDC to the monocomponents in patients presenting to clinical practice with any symptom of vertigo, regardless of origin.

Similar to Hahn 2006, the primary efficacy variable was the change in mean vertigo score (MVS) at week 4. The MVS was calculated by adding the individual scores recorded for each of the 12 vertigo symptoms by patients using a 5 point VAS (0=not present, 4=very strong), divided by 12. Secondary efficacy endpoints were the change in severity of vegetative symptoms associated with vertigo using the same VAS and the Unterberger and Romberg lateral and angular deviation tests, and spontaneous and positional nystagmus and caloric tests with electronystagmography was also performed.

Participants and investigators rated overall efficacy of treatment using a 5 point scale ranging from much improved to deteriorated. All assessments were performed at baseline, after one week of treatment and at 4 weeks.

The incidence, severity and relationship to study medicine of all observed or reported adverse events were recorded. The overall tolerability of treatments was assessed by both the participant and investigator at week 1 and 4 using a 4 point scale (poor to very good).

The decrease in MVS at week 4 was significantly greater in the FDC treatment group (1.37±0.66) compared to 50mg cinnarizine (0.87±0.53; p < 0.001) or 100mg dimenhydrinate alone (0.83±0.66; p < 0.001), even though the dose used for the single components were larger than those used in the FDC.

Compared to placebo, the change in MVS at 4 weeks was 1.37±0.66 in the FDC group, and 0.76±0.48 in placebo (p < 0.001).

Table 3: Change in MVS, point estimates and 95% CI of treatment differences and effect size.

Parameter	FDC (n=61)	Cinnarizine (n=61)	Dimenhydrinate (n=59)	Placebo (n=58)
MVS (SD)				
Baseline	1.85 (0.54)	1.72 (0.52)	1.69 (0.57)	1.74 (0.63)
Week 4	0.45 (0.51)	0.81 (0.58)	0.87 (0.58)	1.01 (0.69)
	1.37 (0.66)	0.87 (0.53)*	0.83 (0.66)*	0.76 (0.48)*
Adjusted mean LS at week 4 (95% CI)	0.43 (0.30, 0.56)	0.86 (0.73, 1.00)**	0.90 (0.76, 1.03)**	0.99 (0.86, 1.13)**
comparator (95% CI)		0.43 (0.25, 0.62)	0.47 (0.28, 0.66)	0.56 (0.38, 0.75)
Cohens difference (95% CI)		0.84 (0.47, 1.21)	0.83 (0.45, 1.20)	1.06 (0.67, 1.45)
Mann-Whitney estimator (95% CI)		0.72 (0.63, 0.80)	0.72 (0.62, 0.80)	0.77 (0.68, 0.84)

*p < 0.001 **0.1% probability that LS mean for FDC is equal to LS mean for comparator

The proportion of participants with no vertigo symptoms (MVS = 0) at week 4 was 21.3% in the FDC group, 6.6% in the cinnarizine group (p = 0.034), 3.4% in the placebo arm (p = 0.005) and 8.5% in the dimenhydrinate group (NS).

The most frequently reported vegetative symptoms of vertigo at baseline were nausea and headache. Nausea improved to a significantly greater degree with FDC compared to other treatments. For the routine balance tests included in the secondary analysis, only the difference in change in lateral sway between FDC and placebo reached statistical significance. In general, the various nystagmus tests indicated no specific treatment effect, or difference between groups.

The primary efficacy endpoint, and the majority of secondary efficacy variables, used to evaluate comparative benefit of the FDC in remaining supportive RCT were similar in all but one of the individual RCT. The primary efficacy endpoint generally used was mean reduction in vertigo score, which was based on a combination of type and intensity of vertigo symptoms experienced by the participants. One study evaluated the intensity of vertigo symptoms, however the classification system used to assess this parameter was less comprehensive compared to the other 8 studies. The supportive efficacy studies in all cases showed at least a trend towards greater efficacy with the FDC given three times daily compared to either active when administered as 20 or 50mg cinnarizine or 40 or 100mg dimenhydrinate.

All but one of the 9 RCT also evaluated the comparative safety of the FDC. In general, the studies found no statistically or clinically significant difference in the safety profile of the FDC compared to the equi-dose monotherapy components, based on comparative adverse event analysis. Participant assessment of overall tolerability generally indicated high levels of satisfaction, with little difference (slightly favoring FDC) between the FDC and equi-dose monocomponent cinnarizine and dimenhydrinate formulations, and better than the individual high dose formulations.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration. Diphenhydramine and cinnarizine are rapidly absorbed from the gastro-intestinal tract. Maximum plasma concentrations (C_{max}) of cinnarizine and diphenhydramine are reached in humans within 2-4 hours.

The plasma elimination half-lives of diphenhydramine, and possibly also cinnarizine, are known to be age-dependent, but typically range from 4-5 hours for both substances, when given either alone or as the combination product.

Animal and human studies show active uptake and accumulation of diphenhydramine in the brain. This effect was not seen in animal studies using cinnarizine.

Metabolism

Cinnarizine and diphenhydramine are extensively metabolised in the liver. The metabolism of cinnarizine involves ring hydroxylation reactions, mainly catalysed by CYP2D6 and to a lesser extent by CYP2B6, and α -dealkylation reactions catalysed by CYP2CP and CYP1A2. The major pathway of diphenhydramine metabolism is the sequential α -demethylation of the tertiary amine, which is mainly catalysed by CYP2D6.

Excretion

Cinnarizine is mainly eliminated via the faeces (40-60%) and to a lower extent also in urine, mainly in the form of metabolites conjugated with glucuronic acid. The major route of elimination of diphenhydramine is in the urine, mainly in the form of metabolites, with the deaminated compound, diphenylmethoxy acetic acid, being the predominant metabolite (40-60%).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of cinnarizine/dimenhydrinate combination tablets has not been fully evaluated.

Carcinogenicity

The carcinogenic potential of cinnarizine/dimenhydrinate combination tablets has not been fully evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CIZINATE tablets also contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, maize starch, hypromellose, colloidal anhydrous silica, purified talc and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities have not been assessed.

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 25 C.

6.5 NATURE AND CONTENTS OF CONTAINER

CIZINATE 20 mg/40 mg tablets are available in OPA-Al-PVC/Al blisters packs of 20, 30, 50 and 100 tablets.

Not all pack sizes may be marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

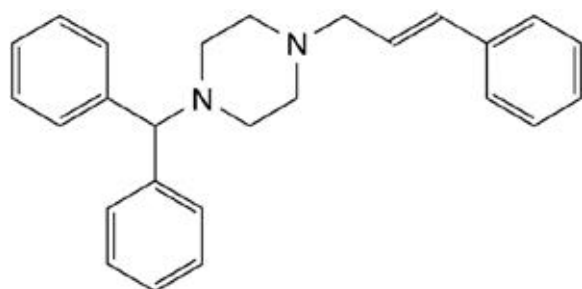
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical Name: ()-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine

Structure:

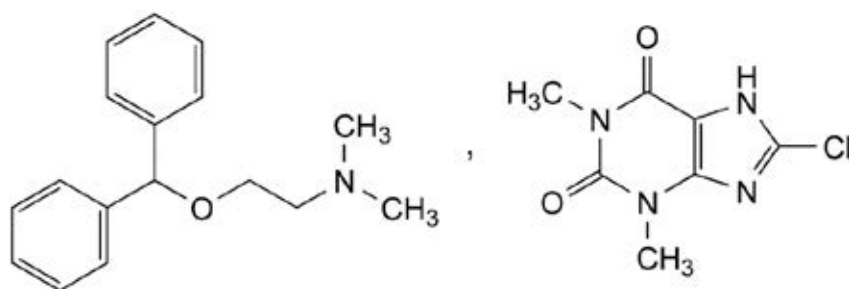


Molecular Formula: $C_{26}H_{28}N_2$

Molecular Weight: 368.5

Chemical Name: Diphenhydramine [2-(diphenylmethoxy)- , -dimethylethanamine] 8-chlorotheophylline (8-chloro-1,3-dimethyl-3,7-dihydro-1 -purine-2,6-dione)

Structure:



Molecular Formula: $C_{24}H_{28}ClN_5O_3$

Molecular Weight: 470.0

CAS number

Cinnarizine: 298-57-7

Dimenhydrinate: 523-87-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Southern Cross Pharma Pty Ltd
Suite 5/118 Church Street
Hawthorn
Victoria 3122

9 DATE OF FIRST APPROVAL

08/01/2019

10 DATE OF REVISION

Not Applicable.