

1 NAME OF THE MEDICINE

Cyproheptadine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of cyproheptadine hydrochloride as the active ingredient.

Excipients with known effect: lactose monohydrate

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

3 PHARMACEUTICAL FORM

White, flat circular bevel edged tablet containing 4 mg of cyproheptadine hydrochloride. Marked 'P4' on one side, scored on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PERIACTIN (cyproheptadine hydrochloride) is a serotonin and histamine antagonist with anticholinergic and sedative effects.

As an anti-allergic-antipruritic

PERIACTIN has a wide range of anti-allergic and anti-pruritic activity and can be used successfully in the treatment of acute and chronic allergies and pruritus, such as: dermatitis, including neurodermatitis and neurodermatitis circumscripta, eczema, eczematoid dermatitis, dermatographism, mild local allergic reactions to insect bites, hay fever and other seasonal rhinitis, perennial allergic and vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods, urticaria, angioneurotic oedema, drug and serum reactions, anogenital pruritus and pruritus of chickenpox.

PERIACTIN may be used as therapy for anaphylactic reactions, adjunctive to adrenalin and other standard measures after the acute manifestations have been controlled.

In migraine and vascular types of headache

PERIACTIN has been reported to have beneficial effects in a significant number of patients diagnosed as having vascular types of headache, such as migraine and histamine cephalgia. Many patients who have not been able to obtain adequate relief from any other agent have reported amelioration of symptoms with PERIACTIN. The characteristic headache and feeling of malaise may disappear within an hour or two after the first dose.

4.2 DOSE AND METHOD OF ADMINISTRATION

Children Under 2 years of Age

There is no recommended dosage schedule for children under 2 years of age.

ALLERGIES AND PRURITUS

Dosage must be individualised. Since the anti-allergic effect of a single dose usually lasts four to six hours, the daily requirement should be given in divided doses three times a day or as often as necessary to provide continuous relief.

Adults

The therapeutic range is from 4 mg to 20 mg a day, the majority of patients requiring 12 mg to 16 mg a day. An occasional patient may require as much as 32 mg a day for adequate relief. It is suggested that dosage be

initiated with 4 mg three times a day and adjusted according to the size and response of the patient. The dosage is not to exceed 32 mg a day.

Children (7 - 14 years)

The usual dosage is 4 mg three times a day. This dosage may be adjusted as necessary according to the size and response of the patient. If an additional dose is required, it should be taken preferably at bedtime. The dosage is not to exceed 16 mg a day.

Children (2 - 6 years)

It is suggested that dosage be initiated with 2 mg two or three times a day and adjusted as necessary according to the size and response of the patient. If an additional dose is required, it should be taken at bedtime. The total dosage is not to exceed 12 mg a day.

FOR MIGRAINE AND VASCULAR TYPES OF HEADACHE

For prophylaxis or treatment, the recommended dosage is 4 mg initially, repeated in 1/2 hour if necessary; not to exceed 8 mg in a 4 to 6 hour period. Relief is usually obtained in responsive patients with 2 doses (total 8 mg) and maintained with 4 mg every 4 to 6 hours.

4.3 CONTRAINDICATIONS

Cyproheptadine should not be used for therapy of an acute asthmatic attack.

Newborn or Premature Infants

This drug should not be used in newborn or premature infants. Use in infants has been associated with apnoea, cyanosis, and respiratory difficulty.

Nursing Mothers

Because of the higher risk of antihistamines for infants generally, and for newborn and prematures, in particular, antihistamine therapy is contraindicated in nursing mothers.

Other Conditions

- . Hypersensitivity to cyproheptadine and other drugs of similar chemical structure
- . Monoamine oxidase inhibitor therapy (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- . Angle-closure glaucoma
- . Stenosing peptic ulcer
- . Symptomatic prostatic hypertrophy
- . Bladder neck obstruction
- . Pyloroduodenal obstruction
- . Elderly, debilitated patients

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Antihistamines should not be used to treat lower respiratory tract symptoms including those of acute asthma.

Use in the Elderly

Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

Paediatric Use

Safety and effectiveness in children below the age of two years have not been established.

Overdose of antihistamines, particularly in infants and children, may produce hallucinations, central nervous system depression, convulsions, respiratory and cardiac arrest, and death.

Antihistamines may diminish mental alertness; conversely, particularly in the young child, they may occasionally produce excitation.

Effects on Laboratory Tests

No data available.

Newborn or Premature Infants

(See section 4.3 CONTRAINDICATIONS)

Other

Rarely, prolonged therapy with antihistamines may cause blood dyscrasias.

Cyproheptadine has an atropine-like action and, therefore, should be used with caution in patients with:

- . History of bronchial asthma
- . Increased intraocular pressure
- . Hyperthyroidism
- . Cardiovascular disease
- . Hypertension

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g.: hypnotics, sedatives, tranquillisers, anti-anxiety agents.

Drugs with anti-serotonin activity, such as cyproheptadine, may interfere with serotonin- enhancing anti-depressant drugs.

Cyproheptadine may cause a false positive test result for tricyclic antidepressant drugs when evaluating a drug screen (e.g. urine, serum).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproduction studies have been performed in rabbits, mice, and rats at doses up to 32 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyproheptadine. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cyproheptadine at about 10 times the human dose had no effect on fertility in a two-litter study in rats or a two-generation study in mice.

Use in Pregnancy

Pregnancy Category: A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

The use of any drug in pregnancy or in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards to the embryo or fetus.

Use in Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from PERIACTIN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (See section 4.3 CONTRAINDICATIONS).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cyproheptadine may cause drowsiness and may increase the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The side effects that appear frequently are drowsiness and somnolence. Many patients who complain initially of drowsiness may no longer do so after the first three or four days of continuous administration.

Table 1: Adverse reactions which have been reported with the use of antihistamines:

<u>Central Nervous System</u>	Sedation, sleepiness (often transient), dizziness, disturbed co-ordination, confusion, restlessness, excitation, nervousness, tremor, irritability, aggressive behaviour, insomnia, paraesthesias, neuritis, convulsions, euphoria, hallucinations, hysteria, faintness
<u>Integumentary</u>	Allergic manifestation of rash and oedema, excessive perspiration, urticaria photosensitivity
<u>Special Senses</u>	Acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus
<u>Cardiovascular</u>	Hypotension, palpitation, tachycardia, extrasystoles, anaphylactic shock
<u>Haematological</u>	Haemolytic anaemia, leucopenia, agranulocytosis, thrombocytopenia
<u>Digestive System</u>	Cholestasis, hepatic failure, hepatitis, hepatic function abnormality dryness of mouth, epigastric distress anorexia, nausea vomiting diarrhoea constipation jaundice
<u>Genitourinary</u>	Frequency of micturition, difficult micturition urinary retention, early menses
<u>Respiratory</u>	Dryness of nose and throat, thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness, epistaxis
<u>Miscellaneous fatigue</u>	Chills headache, increased appetite/weight gain

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 Poison Information Centre on 13 11 26 (Australia).

Signs and Symptoms

Antihistamine overdosage reactions may vary from central nervous system depression or stimulation to convulsions respiratory and cardiac arrest, and death especially in infants and children. Also, atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing, etc.) as well as gastrointestinal symptoms may occur.

Treatment

Treatment should be supportive and symptomatic. Activated charcoal may reduce absorption of the medicine 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.

Precautions against aspiration must be taken especially in infants and children.

When life threatening CNS signs and symptoms are present, intravenous physostigmine salicylate may be considered. Dosage and frequency of administration are dependent on age, clinical response, and recurrence after response. (See package circulars for physostigmine products.)

Saline cathartics, such as milk of magnesia, draw water into the bowel by osmosis and therefore, are valuable for their action in rapid dilution of bowel content.

Stimulants should not be used. Vasopressors may be used for hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

PERIACTIN (cyproheptadine HCL) is a serotonin and histamine antagonist with anticholinergic and sedative effects. Anti-serotonin and antihistamine drugs appear to compete with serotonin and histamine, respectively for receptor sites.

Animal studies have shown cyproheptadine hydrochloride to be an effective serotonin and histamine antagonist, comparable, in general, to that of the most active known substances.

Cyproheptadine hydrochloride antagonises the following effects of serotonin in laboratory animals:

bronchoconstrictor (guinea pig) vasodepressor (dog) spasmogenic (isolated rat uterus)
oedema (rat)
lethal (Haemophilus pertussis-treated mouse)

In all these effects, cyproheptadine hydrochloride approaches, equals or surpasses the activity of specific serotonin antagonists, such as 1-benzyl-2-methyl-5-methoxytryptamine (BAS) and 1-benzyl-2-methyl-5-hydroxytryptamine (BMS). In contrast, specific antihistamines, even the most potent, show little or no serotonin antagonism. Thus, cyproheptadine hydrochloride must be considered a serotonin antagonist as well as a histamine antagonist.

Cyproheptadine hydrochloride antagonises or blocks the following effects of histamine in laboratory animals:

bronchoconstrictor (guinea pig) vasodepressor (dog)
spasmogenic (isolated guinea pig ileum)
anaphylactic shock, active and passive (guinea pig, mouse) increased gastric secretion (Heidenhain pouch dog)

That cyproheptadine hydrochloride protects both guinea pigs and mice against anaphylactic shock is unusual. In guinea pigs, the pulmonary aspects of anaphylactic shock are attributable to the release of endogenous histamine and can be controlled by substances with specific antihistaminic activity. In mice, however, where histamine release seems to be less important and serotonin release may be involved, specific antihistamines are of little value in protecting against anaphylaxis. Thus, the protective effect of cyproheptadine hydrochloride in mice may be an anti-serotonin effect.

The inhibitory effect of cyproheptadine hydrochloride in histamine-induced gastric secretion is also unusual because specific antihistamines do not influence this effect of histamine.

Because of its marked activity as an antagonist of serotonin and histamine in laboratory animals, cyproheptadine hydrochloride was evaluated in man in situations where standard antihistamines are not effective.

In one evaluation, skin reactions were induced in test subjects by the intra dermal injection of histamine, serotonin, and histamine-releasing substances, such as Compound 48-80. The wheals and flares resulting from the injections were observed, as well as the degree of blueness of the wheals produced by intravenous injection

of a protein dye, coomassie blue. Coomassie blue was used as an indicator of capillary leakage of plasma proteins because of its propensity for plasma binding and its safety for use in man. Cyproheptadine hydrochloride and two standard antihistamines were administered orally in moderate therapeutic doses. Only cyproheptadine hydrochloride led to a suppression of the whealing responses and the capillary damage demonstrated by the bluing reaction.

Acute and chronic toxicity studies in various laboratory animals indicate that cyproheptadine hydrochloride has an adequate margin of safety. In doses far greater than those in the therapeutic range, ataxia, sedation and tachycardia can be produced, but other objective signs of toxicity are not evident.

The oral LD₅₀ of cyproheptadine is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively.

There was no evidence of histomorphological changes in the various organs when doses approximating subacute lethal doses were administered to dogs, monkeys, rabbits, and mice. Twelve months of oral toxicity studies in dogs did not reveal functional or anatomical changes. In chronic toxicity studies in rats, only at dosages of 10 to 12 mg/kg/day, far in excess (approximately 200 times) of those required for pharmacodynamic effects, was reversible vacuolisation of the beta cells of the pancreatic islets noted. This was not observed in the other four species of animals used in the toxicity studies. After six months of continuous drug administration there was no evidence derangement of carbohydrate metabolism in man, as measured by serial blood sugar determinations and glucose tolerance tests.

Cyproheptadine hydrochloride has central nervous system effects in laboratory animals, including anticonvulsant and anti-tremor activity and behavioural effects. It has weak peripheral anticholinergic activity and moderate local anaesthetic action. It exerts highly effective protection against burn shock in mice. Most of these properties are evident only with doses much larger than those used in therapy. In the rat, for instance, behavioural effects are produced only by doses 50-100 times greater than those required to produce anti serotonin activity.

Cyproheptadine is not a hormone, but has effects on certain endocrine systems in man, possibly as a result of its anti-serotonin activity. It acts centrally to reduce ACTH secretion and thus tends to cause modest reductions in adrenal corticosteroid output and plasma cortisol levels. This effect has been studied with variable results in the treatment of Cushing's disease and Nelson's syndrome. Cyproheptadine may reduce plasma growth hormone levels during the early phase of sleep and in response to exogenous arginine or insulin but does not reduce linear growth. Neither has an increase in linear growth in undersized children been demonstrated beyond that which would normally be expected as a result of improved nutrition. These endocrine effects of cyproheptadine have not been shown to have adverse clinical significance.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Excretion

After a single 4 mg oral dose of ¹⁴C-labelled cyproheptadine HCl in normal subjects, given as tablets or syrup, 2-20% of the radioactivity was excreted in the stools. Only about 34% of the stool radioactivity was unchanged drug, corresponding to less than 5.7% of the dose. At least 40% of the administered radioactivity was excreted in the urine. No significant difference in the mean urinary excretion exists between tablet and syrup formulations. No detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of a PERIACTIN syrup formulation. The principal metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine. Elimination is diminished in renal insufficiency.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Cyproheptadine has not been evaluated in long term carcinogenicity studies. Cyproheptadine did not produce chromosome damage in human lymphocytes or fibroblasts *in vitro*; high dose (10^{-4} M) were cytotoxic.

Mutagenicity

Cyproheptadine did not have any mutagenic effect in the Ames microbial mutagen test; concentrations of above 500 mcg/plate inhibited bacterial growth.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize starch, pregelatinised maize starch, calcium hydrogen phosphate dihydrate, lactose monohydrate, magnesium stearate.

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Blister pack

Pack sizes: 50 or 100 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 62384 – PERIACTIN cyproheptadine hydrochloride (as sesquihydrate) 4mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

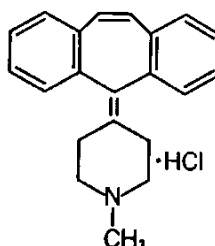
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Cyproheptadine hydrochloride, is a white to slightly yellowish crystalline solid, with a molecular weight of 350.89, which is soluble in water to the extent of about 4 mg per ml, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform, and practically insoluble in ether.

It is the sesquihydrate of 4-(5H-dibenzo [a,d] cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride. The empirical formula of the anhydrous salt is $C_{21}H_{21}N \cdot HCl$ and the structural formula of the anhydrous salt is:

Chemical Structure



CAS Number

969-33-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR**Viatrix Pty Ltd**

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatrix.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

29/01/1998

10 DATE OF REVISION

26/10/2021

Summary Table of Changes

Section Changed	Summary of New Information
6.5	Insert AUST R numbers
8	Update sponsor's details

PERIACTIN® is a Viatrix company trade mark

PERIACTIN_pi\SOct21/00