Name of Medicine

PERIACTIN®

cyproheptadine hydrochloride

4mg tablets

Presentation

A round white flat tablet with a bevelled edge engraved MSD 62 on one side and scored on the other. The diameter is 7.9mm.

Therapeutic Class

PERIACTIN is a serotonin and histamine antagonist.

Indications

As an Antiallergic-Antipruritic

PERIACTIN has a wide range of antiallergic and antipruritic 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, medicine and serum reactions, anogenital pruritus and pruritus of chickenpox.

PERIACTIN may be used as therapy for anaphylactic reactions, adjunctive to epinephrine 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 cephalalgia. 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.

Dosage and Administration

Dosage Recommendations

PERIACTIN is not recommended for children under two years.

<u>Allergies and Pruritus</u>

Dosage must be individualised. Since the antiallergic 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.

<u>Adults</u>

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

according to the size and response of the patient. The dosage is not to exceed 32mg a day.

Children (7 to 14 years)

The usual dosage is 4mg two or 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 16mg a day.

Children (2 to 6 years)

It is suggested that dosage be initiated with 2mg 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 12mg a day.

For Migraine and Vascular Types of Headache

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

Contraindications

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

Newborn or Premature Infants

This medicine 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 medicines of similar chemical structure
- Monoamine oxidase inhibitor therapy (see Medicine Interactions)
- Angle-closure glaucoma
- Stenosing peptic ulcer
- Symptomatic prostatic hypertrophy
- Bladder neck obstruction
- Predisposition to urinary retention
- Pyloroduodenal obstruction
- Elderly, debilitated patients

Warning and Precautions

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

Paediatric Use

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

Overdosage 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.

Newborn or Premature Infants (see Contraindications)

Pregnancy

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

Nursing Mother

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

Activities Requiring Mental Alertness

Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies have not been done with cyproheptadine.

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.

Cyproheptadine did not produce chromosome damage in human lymphocytes or fibroblasts in vitro; high doses (10^{-4}M) were cytotoxic. Cyproheptadine did not have any mutagenic effect in the Ames microbial mutagen test; concentrations of above 500 mcg/plate inhibited bacterial growth.

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 foetus 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 medicine should be used during pregnancy only if clearly needed.

Cyproheptadine is not a hormone, but has effects on certain endocrine systems, in humans possibly as a result of its antiserotonin 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.

Adverse 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.

Adverse reactions which have been reported with the use of antihistamines are as follows:

Central Nervous System: sedation, sleepiness (often transient), dizziness, disturbed coordination, confusion, restlessness, excitation, nervousness, tremor, irritability, aggressive behaviour, insomnia, paresthesias, neuritis, convulsions, euphoria, hallucinations, hysteria, faintness

Integumentary: allergic manifestation of rash and oedema, excessive perspiration, urticaria, photosensitivity

Special Senses: acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus

Cardiovascular: hypotension, palpitation, tachycardia, extrasystoles, anaphylactic shock

Haematologic: haemolytic anaemia, leukopaenia, agranulocytosis, thrombocytopenia,

Digestive System: cholestasis, hepatic failure, hepatitis, hepatic function abnormality dryness of mouth, epigastric distress, anorexia, nausea, vomiting, diarrhoea, constipation, jaundice

Genitourinary: frequency of micturition, difficult micturition, urinary retention, early menses

Respiratory: dryness of nose and throat, thickening of bronchial secretions, tightness of chest, and wheezing, nasal stuffiness

Miscellaneous: fatigue, chills, headache, increased appetite/weight gain

Medicine Interactions

MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines. Antihistamines may have additive effects with alcohol and other CNS depressants, eg, hypnotics, sedatives, tranquillisers, antianxiety 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).

Overdosage

Antihistamine overdosage reactions may vary from central nervous system depression or stimulation to convulsions 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.

If vomiting has not occurred spontaneously the patient should be induced to vomit if conscious with syrup of ipecac.

If the patient is unable to vomit, perform gastric lavage followed by activated charcoal. Isotonic or 1/2 isotonic saline is the lavage of choice. 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 to treat hypotension.

Actions

PERIACTIN* (cyproheptadine hydrochloride, MSD) is a serotonin and histamine antagonist with anticholinergic and sedative effects. Antiserotonin 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 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-methoxy-tryptamine (BAS) and 1-benzyl-2-methyl-5-hydroxy-tryptamine (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 antiserotonin 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 intradermal 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 LD_{50} of cyproheptadine is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively.

There was no evidence of histomorphologic 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 of 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 antitremor 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 to 100 times greater than those required to produce antiserotonin activity.

Pharmacokinetics

After a single 4 mg oral dose of ^{14}C-labelled cyproheptadine HCl in normal subjects, given as tablets, 2-20% of the radioactivity was excreted in the stools. Only about 34% of the stool radioactivity was unchanged medicine, corresponding to less than 5.7% of the dose. At least 40% of the administered radioactivity was excreted in the urine. The principal metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine. Elimination is diminished in renal insufficiency.

Pharmaceutical Precautions

Keep in a cool place protected from sunlight and excessive heat.

Medicine Classification

Pharmacy Only Medicine.

Package Quantities

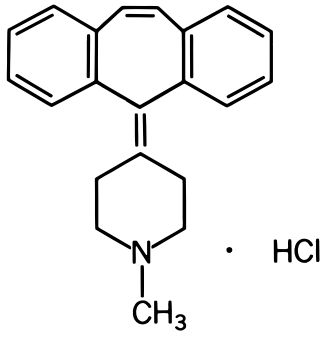
100 tablets per bottle.

Further Information

Chemistry

PERIACTIN (cyproheptadine HCl, MSD) is an antihistaminic and antiserotonergic agent.

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 $C_{21}H_{21}N.HCl$ and the structural formula of the anhydrous salt is:



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