CYPROHEPTADINE- cyproheptadine syrup
Pharmaceutical Associates, Inc.

Cyproheptadine Hydrochloride Syrup
[Cyproheptadine Hydrochloride Oral Solution, USP]

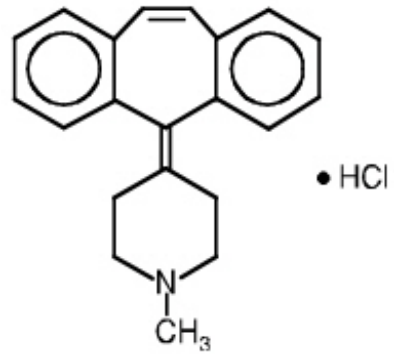
Rx ONLY

DESCRIPTION

Each 5 mL (one teaspoonful) contains: Cyproheptadine hydrochloride 2 mg. Alcohol 5%.

Inactive ingredients: citric acid, D&C Yellow No.10, peppermint flavor, purified water, sodium benzoate, sodium citrate and sucrose.

Cyproheptadine hydrochloride is an antihistaminic and antiserotonergic agent. Cyproheptadine hydrochloride is a white to slightly yellowish, crystalline solid, with a molecular weight of 350.88, which is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform and practically insoluble in ether. It is the sesquihydrate of 4-(5*H*-Dibenzo [*a,d*] cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride. The molecular formula of the anhydrous salt is $C_{21}H_{21}N$ • HCl and the structural formula of the anhydrous salt is:



CLINICAL PHARMACOLOGY

Cyproheptadine 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.

Pharmacokinetics and Metabolism

After a single 4 mg oral dose of ^{14}C-labeled cyproheptadine HCl in normal subjects, given as tablets or oral solution, 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 detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of cyproheptadine oral solution. The principal metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine. Elimination is diminished in renal insufficiency.

INDICATIONS AND USAGE

Perennial and seasonal allergic rhinitis

Vasomotor rhinitis

Allergic conjunctivitis due to inhalant allergens and foods

Mild, uncomplicated allergic skin manifestations of urticaria and angioedema

Amelioration of allergic reactions to blood or plasma

Cold urticaria

Dermatographism

As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled.

CONTRAINDICATIONS

Newborn or Premature Infants

This drug should *not* be used in newborn or premature infants.

Nursing Mothers

Because of the higher risk of antihistamines for infants generally and for newborns 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 Drug Interactions)

Angle-closure glaucoma

Stenosing peptic ulcer

Symptomatic prostatic hypertrophy

Bladder neck obstruction

Pyloroduodenal obstruction

Elderly, debilitated patients

WARNINGS

Children

Overdosage of antihistamines, particularly in infants and children, may produce hallucinations, central nervous system depression, convulsions and death.

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

CNS Depressants

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers, antianxiety agents.

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.

PRECAUTIONS

General

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

Information for Patients

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

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

Drug 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, tranquilizers, anti-anxiety agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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.

Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rabbits, mice and rats at oral or subcutaneous doses up to 32 times the maximum recommended human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyproheptadine. Cyproheptadine has been shown to be fetotoxic in rats when given by intraperitoneal injection in doses four times the maximum recommended human oral dose. Two studies in pregnant women, however, have not shown that cyproheptadine increases the risk of abnormalities when administered during the first, second and third trimesters of pregnancy. No teratogenic effects were observed in any of the newborns. Nevertheless, because the studies in humans cannot rule out the possibility of harm, cyproheptadine should be used during pregnancy only if clearly needed.

Nursing Mothers

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 cyproheptadine, 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 CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients below the age of two years have not been established. (see CONTRAINDICATIONS, Newborn or Premature Infants, and WARNINGS, Children).

ADVERSE REACTIONS

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

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

Integumentary: Allergic manifestation of rash and edema, excessive perspiration, urticaria, photosensitivity.

Special Senses: Acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus.

Cardiovascular: Hypotension, palpitation, tachycardia, extrasystoles, anaphylactic shock.

Hematologic: Hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia.

Digestive System: Dryness of mouth, epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation, jaundice.

Genitourinary: Urinary frequency, difficult urination, 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.

OVERDOSAGE

Antihistamine overdosage reactions may vary from central nervous system depression to stimulation especially in 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 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, as milk of magnesia, by osmosis draw water into the bowel 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.

The oral LD_{50} of cyproheptadine is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND THE RESPONSE OF THE PATIENT.

Although intended primarily for administration to children, the oral solution is also used for administration to adults who cannot swallow tablets.

Children

The total daily dosage for children may be calculated on the basis of body weight or body area using approximately 0.25 mg/kg/day (0.11 mg/lb/day) or 8 mg per square meter of body surface (8 mg/m^2).

Age 2 to 6 years

The usual dose is 2 mg (one teaspoonful) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 12 mg a day.

Age 7 to 14 years

The usual dose is 4 mg (two teaspoonfuls) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 16 mg a day.

Adults

The total daily dose for adults should not exceed 0.5 mg/kg/day (0.23 mg/lb/day). The therapeutic range is 4 to 20 mg a day, with the majority of patients requiring 12 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 (two teaspoonfuls) three times a day and adjusted according to the size and response of the patient.

HOW SUPPLIED

Cyproheptadine Hydrochloride Syrup (Cyproheptadine Hydrochloride Oral Solution, USP) (2 mg/5 mL), a pale yellow, peppermint flavored liquid, is available in the following oral dosage forms:

NDC 0121-0788-16 – Bottles of 16 fl oz (473 mL)

NDC 0121-4788-05 – 5 mL Unit Dose Cups, 10 cups per tray

NDC 0121-4788-10 – 10 mL Unit Dose Cups, 10 cups per tray

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Pharmaceutical Associates, Inc.
Greenville, SC 29605

www. paipharma.com

R03/12

PRINCIPAL DISPLAY PANEL - 473 mL Bottle Label

NDC 0121-0788-16

Cyproheptadine Hydrochloride Syrup
(Cyproheptadine Hydrochloride Oral Solution,USP)

2 mg/5 mL

Each 5 mL (one teaspoonful) contains:
Cyproheptadine hydrochloride..... 2 mg
Alcohol 5%

Rx ONLY

16 fl oz (473 mL)

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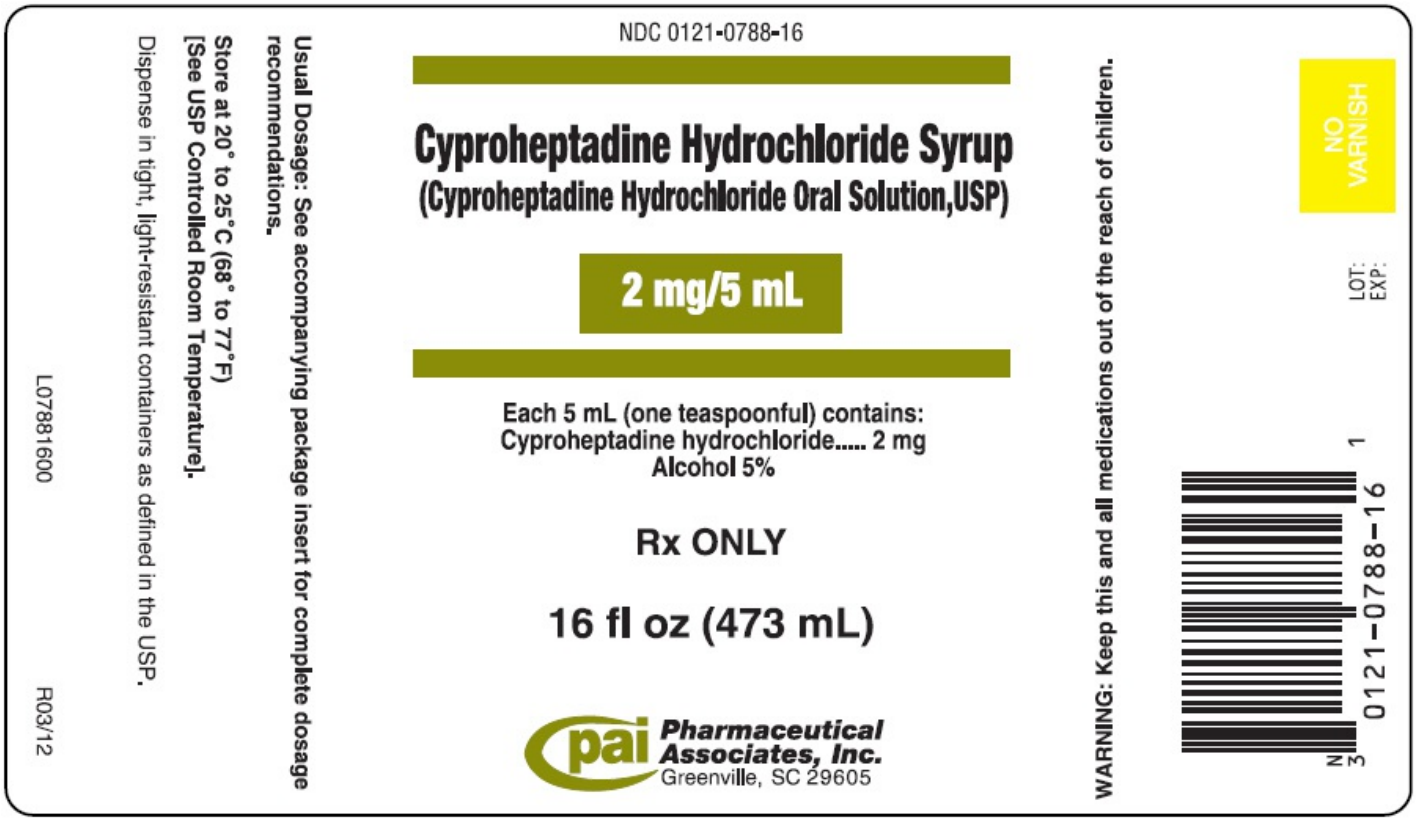
Pharmaceutical
Associates, Inc.
Greenville, SC 29605



PRINCIPAL DISPLAY PANEL - 5 mL Cup Label

Delivers **5 mL**
NDC 0121-4788-05

CYPROHEPTADINE HYDROCHLORIDE SYRUP
(Cyproheptadine Hydrochloride Oral Solution,USP)

2 mg/5 mL
CONTAINS ALCOHOL 5%
FOR INSTITUTIONAL USE ONLY

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.

Rx ONLY

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

A47880500

CYPROHEPTADINE

cyproheptadine syrup

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0121-0788
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CYPROHEPTADINE (UNII: 2YHB6175DO) (CYPROHEPTADINE - UNII:2YHB6175DO)	CYPROHEPTADINE	2 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
ALCOHOL (UNII: 3K9958V90M)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
WATER (UNII: 059QF0KO0R)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	

SUCROSE (UNII: C151H8M554)	

Product Characteristics			
Color	YELLOW (PALE)	**Score**	
Shape		**Size**	
Flavor	PEPPERMINT	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0121-0788-16	473 mL in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091295	07/29/2013	

CYPROHEPTADINE

cyproheptadine syrup

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0121-4788
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CYPROHEPTADINE (UNII: 2YHB6175DO) (CYPROHEPTADINE - UNII:2YHB6175DO)	CYPROHEPTADINE	2 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
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D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
WATER (UNII: 059QF0KO0R)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SUCROSE (UNII: C151H8M554)	

Product Characteristics			
Color	YELLOW (PALE)	**Score**	

Shape		**Size**	
Flavor	PEPPERMINT	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0121-4788-05	4 in 1 CASE		
1		10 in 1 TRAY		
1		5 mL in 1 CUP, UNIT-DOSE		
2	NDC:0121-4788-10	4 in 1 CASE		
2		10 in 1 TRAY		
2		10 mL in 1 CUP, UNIT-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091295	07/29/2013	

Labeler - Pharmaceutical Associates, Inc. (044940096)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmaceutical Associates, Inc.		097630693	MANUFACTURE(0121-0788, 0121-4788)

Revised: 7/2013 Pharmaceutical Associates, Inc.