**3. Pharmaceutical form** Oral Solution

**4. Clinical particulars**

**4.1 Therapeutic indications**

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.

- 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.

**4.2 Posology and method of administration**

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

Although intended primarily for administration to children, the syrup 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/m2).

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 teaspoonful) 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 teaspoonful) three times a day and adjusted according to the size and response of the patient.

### 4.3 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.

- 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

**Warnings**

**Paediatric Patients**

Overdosage of antihistamines, particularly in infants and young 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.

**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 (see precautions, geriatric use).

**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.

**4.5 Interaction with other medicinal products and other forms of interaction**

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, 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**

**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.

## 4.7 Effects on ability to drive and use machines

None.

## 4.8 Undesirable effects

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**

Cholestasis, hepatic failure, hepatitis, hepatic function abnormality, 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.

### 4.9 Overdose

Antihistamine over dosage reactions may vary from central nervous system depression to stimulation especially in paediatric patients. 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 patient is unable to vomit, perform gastric lavage followed by activated charcoal. Isotonic or ½ 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. 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.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistaminic.

ATC code: R06AX02

**Mode of action**

Cyproheptadine appears to exert its antihistamine and antiserotonin effects by competing with free histamine and serotonin for binding at their respective receptors. Antagonism of serotonin on the appetite center of the hypothalamus may account for cyproheptadine's ability to stimulate the appetite.

### 5.2 Pharmacokinetic properties

**Absorption:** A single study examining the difference in absorption of orally administered versus sublingually administered cyproheptadine in five healthy males demonstrated a mean Cmax of 30.0 mcg/L and 4.0 mcg/L, respectively, and a mean AUC of 209 mcg.h/L and 25 mcg.h/L, respectively. The Tmax of orally and sublingually administered cyproheptadine was 4 hours and 9.6 hours, respectively.

**Distribution:** All compounds administered had large distribution volumes and were most entirely excreted as DMCPHepo (desmethyl cyproheptadine epoxide) in urine; this excretion continued for a long time.

**Elimination:** Approximately 2-20% of the radioactivity from an orally administered radio-labeled dose of cyproheptadine is excreted in the feces, of which approximately 34% is unchanged parent drug (less than 5.7% of the total dose). At least 40% of radioactivity is recovered in the urine.

**Special populations:** Insufficient experience in patients ≥65 years of age to determine whether geriatric patients respond differently than younger adults; clinical experience has not revealed age-related differences. Select dosage with caution (usually starting at low end of dosage range) because of age-related decreases in hepatic, renal, and/or cardiac function and concomitant disease and drug therapy.

**Elderly:** Avoid use in the elderly because of the high incidence of anticholinergic effects; may exacerbate existing lower urinary conditions or benign prostatic hyperplasia; if used, administer at the low end of the dosage range.

### 5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Propylene Glycol USP, Sugar BP, Methyl Paraben BP, Propyl Paraben BP, Aspartame BP, Citric Acid Monohydrate BP, Flavour Mix Fruit IH, Calour Cammel IH, Purified water BP.

### 6.2 Incompatibilities

Not Applicable.

**6.3 Shelf life**

18 Months

**6.4 Special precautions for storage**

Store in a cool, dry & dark place at a temperature below $30^0$C. Protect from light & moisture. Keep the medicine out of reach of children.

**6.5 Nature and contents of container**

Brown coloured flavoured syrupy liquid filled in 100 ml amber colour PET bottle sealed with plain golden colour pp cap. One bottle packed in carton with pack insert.

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. Marketing authorisation holder**

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**8. Marketing authorisation number(s)**

N/A

**9. Date of first authorisation/renewal of the authorisation**

N/A

**10. Date of revision of the text**

N/A