ARPETUMIN® SYRUP

(CYPROHEPTADINE HYDROCHLORIDE BP 2 mg/5 ml)

SUBMITTED BY: NALIS PHARMACEUTICALS LTD

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SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE DRUG PRODUCT

Arpetumin® syrup (Cyproheptadine Hydrochloride BP 2 mg/5 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A golden yellow syrup with banana flavour

Each 5 ml contains:
Cyproheptadine Hydrochloride BP…. **2mg**
Excipients…….. qs

3. PHARMACEUTICAL FORM

Oral syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arpetumin syrup is indicated for 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

Posology

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

Method of administration
For oral administration.

4.3 Contradindications

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.

4.4 Special warnings and precautions for use

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, antianxiety 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 (10-4M) 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.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of two years have not been established.

4.5 Interaction with other drug 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, e.g., hypnotics, sedatives, tranquilizers, antianxiety agents

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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

Breast-feeding
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

Fertility
There are no data available on male and female fertility.

4.7 Effects on ability to drive and use machines

In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

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: 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 to the regulatory bodies such as NAFDAC.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

ATC Code: R06AX02

5.2 Pharmacokinetic properties

After a single 4 mg oral dose of 14C-labeled 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 detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of cyproheptadine syrup. 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

Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats at plasma levels (AUC) 10 times higher than those achieved with clinical doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S/N	Raw Materials	Specifications
1.	Sodium CMC	B.P
2.	Methyl paraben	B.P
3.	Propyl paraben	B.P
4.	Glycerine	B.P
5.	Sugar	B.P
6.	Orange flavour	B.P
7.	Sunset Yellow Colour	B.P
8.	Sodium benzoate	B.P
9	Xanthan gum	BP
10	Tween 80	BP
11	Treated water	B.P

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C, protect from sunlight.

6.5 Nature and contents of container

Bottle made from Amber pet with a tamper evident child resistant closure having a polypropylene outer layer and a polyethylene inner layer. This product is provided with a measuring device (dispensing cup).
Pack Sizes: 200 ml.

6.6 Special precautions for disposal of used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

NAME:
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8. DRUG PRODUCT MANUFACTURER

NAME:
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9. NAFDAC REGISTRATION NUMBER(S):

A11-100035