Summary of Product Characteristics

1. Name of the Medical Product
Trimorix

2. Qualitative & Quantitative Composition:
Each 5 ml contains:
Cyproheptadine Hydrochloride BP equivalent to anhydrous
Cyproheptadine Hydrochloride BP 1.5 mg
Carnitine Hydrochloride .....150 mg
Lysine Hydrochloride BP.....150 mg
Thiamine Hydrochloride BP.....10 mg
Pyridoxine Hydrochloride BP.....10 mg
Cyanocobalamin BP.....100 mcg

Excipient of known effect
Sorbitol 70% solution

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:
Syrup

Visual Description
Brown coloured syrup with flavoured odour

4. Clinical Particulars
4.1 Therapeutic Indications:
Appetite Stimulant Syrup is indicated for:

- Symptomatic relief of allergic conditions including urticaria and angioedema, rhinitis and conjunctivitis, and in pruritic skin disorders.
- Other uses include the management of migraine.

Cyproheptadine has been widely used as an appetite stimulant, including for anorexia nervosa and cachexia, but in the long-term appears to have little value in producing weight gain and such use is no longer generally recommended

4.2 Posology and Method of administration:
Posology
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 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.

Method of Administration For oral administration.

4.3 Contraindications:

Cyproheptadine is contra-indicated in patients hypersensitive to cyproheptadine and other medicines of similar chemical structure; in closed angle glaucoma; in bladder neck obstruction; in symptomatic prostatic hypertrophy; in patients on monoamine oxidase inhibitor therapy; in stenosing peptic ulcer; in pyloroduodenal obstruction; and in the elderly, debilitated patient.

Paediatric use:

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

Acute asthmatic attack:

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

Pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

4.4 Special warnings & precautions for use

Pediatric 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.

Prolonged therapy with cyproheptadine may cause blood dyscrasias.

Due to the atropine-like action of cyproheptadine, it should be used with caution in patients with a history of bronchial asthma, hyperthyroidism, increased intra-ocular pressure, cardiovascular disease and hypertension.

4.5 Interactions with other medicinal products and other forms of Interactions

Monoamine oxidase (MAO) inhibitors may prolong and intensify the anticholinergic effects of cyproheptadine.

Cyproheptadine may have additive effects when combined with alcohol and other CNS depressants, e.g. hypnotics, sedatives, tranquillizers and anxiolytic agents

4.6 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 machine*:
Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable Effects*:
The side-effects that present frequently are drowsiness and somnolence. The drowsiness effect may subside after the first three or four days of continuous administration.
The following adverse reactions have been reported with the use of cyproheptadine:
Neurological: Sedation, sleepiness (often transient), disturbed coordination, dizziness, confusion, restlessness, excitation, nervousness, irritability, tremor, paraesthesiae, insomnia, convulsions, euphoria, hallucinations, faintness, hysteria and neuritis.
Dermatological: Allergic manifestations such as a rash and oedema, photosensitivity, excessive perspiration and urticaria.
Special senses: Blurred vision, tinnitus, diplopia, acute labyrinthitis and vertigo.
Cardiovascular: Tachycardia, palpitations, hypotension, extrasystoles and anaphylactic shock.
Haematological: Heamolytic anaemia, agranulocytosis, leukopenia and thrombocytopenia.
Gastro-intestinal: Dryness of the mouth, anorexia, epigastric distress, nausea and vomiting, diarrhoea, jaundice and constipation.
Genito-urinary: Frequency of micturition, difficult micturition, urinary retention and early menses. Respiratory: Thickening of bronchial secretions, dryness of nose and throat, tightness of chest and wheezing, nasal stuffiness.
Other: Fatigue, rigors, headache and increased appetite/weight gain

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose:
Signs and symptoms of cyproheptadine overdosage may vary from hallucinations and central nervous system depression or stimulation to convulsions and death, especially in infants and children. Atropine-like effects (dry mouth, fixed dilated pupils, flushing, etc), as well as gastrointestinal symptoms may occur.
If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required. If vomiting has not occurred spontaneously, vomiting should be induced if the patient is conscious or the patient should be subjected to gastric lavage. Stimulants should not be used. Hypotension may be treated with vasopressors.

5. Pharmacological properties:
5.1 Pharmacodynamic Properties:
Cyproheptadine is a piperidine antihistamine. Unlike other antihistamines, this drug also antagonizes serotonin receptors. This action makes Cyproheptadine useful in conditions such as vascular headache and anorexia. Cyproheptadine does not prevent the release of histamine but rather competes with free histamine for binding at HA-receptor sites. Cyproheptadine competitively antagonizes the effects of histamine on HA-receptors in the GI tract, uterus, large blood vessels, and bronchial smooth muscle. Most antihistamines possess significant anticholinergic properties, but Cyproheptadine exerts only weak anticholinergic actions. Blockade of central muscarinic receptors appears to account for Cyproheptadine's antiemetic effects, although the exact mechanism is unknown. Cyproheptadine also competes with serotonin at receptor sites in smooth muscle in the intestines and other locations. Antagonism of serotonin on the appetite center of the hypothalamus may account for Cyproheptadine's ability to stimulate appetite. Cyproheptadine also has been used to counter vascular headaches, which many believe are caused by changes in serotonin activity; however it is unclear how Cyproheptadine exerts a beneficial effect on this condition.

5.2 Pharmacokinetics Properties*:
Cyproheptadine is a sedating antihistamine with antimuscarinic, serotonin-antagonist and calciumchannel blocking properties. It competes for H1-receptor sites on effector cells in the GIT, blood vessels and resp tract.
Absorption: Absorbed from the GIT (oral). It is well absorbed when given orally.
Metabolism: Completely hepatic via cytochrome P-450 system and sometimes renal.
Excretion: After a single 4 mg oral dose of14C-labelled cyproheptadine HCl in normal subjects, given as tablets 2% to 20% of the radioactivity was excreted in the stools. At least 40% of the administered radioactivity was excreted in the urine.

5.3 Preclinical safety data
No relevant information other than that specified earlier.

6. Pharmaceutical particulars:
6.1 List of Excipients:
1. Sodium Methyl Hydroxybenzoate BP
2. Sodium Propyl Hydroxybenzoate BP
3. Sodium Benzoate BP
4. Sugar BP
5. Sorbitol 70% Solution BP

6. Glycerine BP
7. Propylene Glycol BP
8. Bronopol BP
9. Colour Caramel USP
10. Flavour Fruit Mix IH
11. Purified Water BP

6.2 Incompatibilities:
None

6.3 Shelf life:
36 months

6.4 Special Precautions for storage:
Store below 30°C. Protect from light. Keep medicines out of reach of children.

6.5 Nature and contents of container:
200 ml amber coloured pet bottle packed in a printed carton along with 10 ml measuring cup and package insert.

6.6 Special precautions for disposal:
None

7. Marketing Authorization Holder:
Signature Healthcare Limited
Cape Business Park,
Along Thika Super Highway,
P.O. Box 66172-00800, Nairobi, KENYA.

Manufacturing Site Address:
Coral Laboratories Ltd.
Plot No. 57/1/16, Bhenslore Dunetha Nani, Daman – 396210, India

8. Marketing Authorization Numbers:
H2022/CTD9114/20249

9. Date of first registration /renewal of the registration:
04/02/2004

10. Date of revision of text:
2022 July 13