For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

COBADEX CZS

1. GENERIC NAME

Pyridoxine Hydrochloride, Nicotinamide, Cyanocobalamin, Folic Acid with Chromium, Zinc and Selenium Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Pyridoxine Hydrochloride IP	3 mg
Nicotinamide IP	100 mg
Cyanocobalamin IP	15 mcg
Folic Acid IP	1500 mcg
Chromium Picolinate IP (equivalent to 31.1mcg of elemental Chromium)	250 mcg
Selenious Acid IP equivalent to elemental Selenium	100 mcg
Zinc Sulphate Monohydrate IP (equivalent to 22.5 mg of elemental Zinc)	61.8 mg

Colours: Titanium Dioxide IP, Lake Ponceau 4R, and Lake Carmoisine.
(Appropriate overages added)

List of Excipients

Dibasic Calcium Phosphate, Maize Starch, Croscarmellose Sodium, Ferric Ammonium Citrate, Methylparaben, Propylparaben, Liquid Paraffin, Magnesium Stearate, Talc, Tabcoat (includes Hypromellose, Ponceau 4R Aluminium lake, Glycerine, Polyvinyl Alcohol, Talc, Polyethylene Glycol/Macrogol, Carmoisine Aluminum Lake, Titanium Dioxide), Purified Water.

3. DOSAGE FORM AND STRENGTH

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

COBADEX CZS is indicated for the treatment of mineral and vitamins deficiency states in adult patients.

4.2 Posology and Method of Administration

Route of Administration

For oral use.

Adults

One tablet once daily.

Duration of treatment depends on the improvement of the deficiency states.

Children

COBADEX CZS is not recommended for pediatric use.

Elderly

There are no relevant data available.

Renal Impairment

Caution should be exercised when administering *COBADEX CZS* to patients with renal disorders (see *section 4.4 Special Warnings and Precautions for Use*).

Hepatic Impairment

Caution should be exercised when administering *COBADEX CZS* to patients with hepatic disorders (see *section 4.4 Special Warnings and Precautions for Use*).

4.3 Contraindications

COBADEX CZS is contraindicated in hypersensitivity to any of the components.

4.4 Special Warnings and Precautions for Use

Concomitant conditions

Caution should be used in case of the following concomitant conditions:

- hepatitis or hepatic disorders,
- kidney disorders.

Vision disorders

Cyanocobalamin (vitamin B_{12}) should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Investigations

Large doses of riboflavin (vitamin B_2) result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests.

Long-term treatment

Long-term use of large doses of pyridoxine (vitamin B_6) is associated with the development of severe peripheral neuropathies; the dose at which these occur is not established.

Treatment preparation and monitoring

COBADEX CZS should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis.

4.5 Drug Interactions

Antibiotics

Zinc supplements reduce the absorption of fluoroquinolones.

Tetracycline antibiotics, other than doxycycline, decrease zinc absorption, they should therefore be administered 2 hours before or 3 hours after the administration of *COBADEX CZS*, in those cases where concomitant use is necessary.

Penicillamine (a chelating agent) may reduce the absorption of zinc.

Penicillamine and antituberculous drugs (such as isoniazid) may increase the requirements for folic acid and pyridoxine (vitamin B_6).

Neomycin used orally may reduce the absorption of vitamin B_{12}.

Folic acid antagonists

Folate deficiency states may be produced by folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim and sulfonamides.

Zinc supplements

Additionally**,** taken zinc supplements reduce the absorption of copper and iron. Prolonged use of high doses of zinc supplements, leads to copper deficiency with associated sideroblastic anaemia and neutropenia.

Glucarpidase

Folate deficiency states may be produced by glucarpidase.

Eltrombopag

Zinc decreases the absorption of eltrombopag to a clinically relevant extent. Thus, eltrombopag (tablets or oral suspension) should be taken at least 2 hours before or 4 hours after mineral supplements containing zinc.

Oral contraceptives

Serum concentration of vitamin B_6, vitamin B_{12} and folic acid may be decreased by use of oral contraceptives.

Levodopa

COBADEX CZS contains vitamin B_6 which reduces the effects of levodopa, but this does not occur if a dopa decarboxylase inhibitor is also given.

Altretamine

COBADEX CZS contains vitamin B_6 which reduces the activity of altretamine.

Antiepileptics

Vitamin B_6 and folic acid has been reported to decrease serum concentrations of phenobarbital and phenytoin.

Antiepileptics may produce folate deficiency states.

Replacement therapy with folinic acid or folic acid may become necessary during antiepileptic therapy in order to prevent development of megaloblastic anaemia.

Concomitant nicotinamide and carbamazepine may decrease carbamazepine clearance.

Hydralazine

Hydralazine may increase the requirements for pyridoxine.

Omeprazole

Omeprazole has been reported to impair the bioavailability of vitamin B_{12}.

Phosphates

Phosphorus-containing preparations may reduce the absorption of zinc.

Alcohol

Alcohol may produce folate deficiency states.

Ascorbate (Vitamin C)

Concomitant intake of ascorbate and *COBADEX CZS* may increase the absorption of chromium and selenium.

Foods

Concomitant intake of chromium with foods rich in phytic acid (unleavened bread, raw beans, seeds, nuts and grains and soy isolates) may decrease the absorption of chromium and zinc.

Concomitant intake of foods rich in oxalic acid (spinach, sweet potatoes, and beans, etc.) may decrease the absorption of zinc.

Iodine

Intake of selenium and iodide may have synergistic activity in treatment of Kashin-Beck disease.

Vitamin E

Intake of vitamin E and selenium may produce synergistic beneficial effects.

Bisphosphonates

Concomitant intake of a bisphosphonate and zinc may decrease the absorption of both the bisphosphonate and zinc.

Calcium

Concomitant calcium intake may decrease zinc absorption.

Copper

Concomitant copper intake may decrease zinc absorption.

L-cysteine, L-histidine, L-methionine, N-acetyl-L-cysteine (NAC)

Concomitant intake of L-cysteine, L-histidine, L-methionine or NAC may enhance the absorption of zinc. Food, rich in cysteine-containing proteins (i.e. animal muscle tissue) may increase the absorption of zinc if ingested concomitantly.

Inositol Hexaphosphate

Concomitant intake of inositol hexaphosphate may decrease the absorption of zinc.

Iron

Concomitant intake of iron may decrease the absorption of both iron and zinc.

Caffeine

Concomitant intake of coffee, caffeinated beverages or caffeine may decrease the absorption of zinc.

Tea

Concomitant intake of tea (tannins) may decrease the absorption of zinc.

Other

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by aminosalicylic acid, histamine H_2-antagonists, and colchicine.

4.6 Use in Special Populations

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

COBADEX CZS should be administered to pregnant women only after consultation with a physician.

Lactation

COBADEX CZS should be administered to breast-feeding mothers only after consultation with a physician.

4.7 Effects on Ability to Drive and Use Machines

There are no clinical data proving that *COBADEX CZS* may have an influence on the ability to drive or use machines.

4.8 Undesirable Effects

Multivitamins are generally well tolerated when used within the recommended dose. The following adverse events have been reported with use of ingredients of *COBADEX CZS*. The frequency of these events cannot be estimated from the available data.

Immune system disorders

Hypersensitivity reactions, urticaria, rash, pruritus, anaphylactic reaction

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, garlic-like breath odor, gastrointestinal discomfort, metallic taste

Nervous system disorders

Headache, dizziness, progression of neurological signs and symptoms of vitamin B_{12} deficiency due to folic acid, irritability, drowsiness

Skin and subcutaneous tissue disorders

Photosensitivity, acute generalized exanthematous pustulosis, hair and nail brittleness and loss, skin rash, dermatitis acneiform and dermatitis bullous.

Metabolic disorders

Diabetogenic effects

4.9 Overdose

Overdose of *COBADEX CZS* can lead to the following symptoms and signs.

Symptoms and signs

Symptoms include: Sensory neuropathy, nausea, vomiting, gastrointestinal discomfort, abdominal pain, loss of appetite, breast soreness, photosensitivity, elevations in liver tests and liver damage, including jaundice and parenchymal liver cell injury and dysfunction, headache, dizziness, sleep disturbances, mental changes, other gastrointestinal effects, decreased HDL cholesterol, copper deficiency leading to hypochromic microcytic anemia, immune suppression, hair and nail brittleness and loss, thickened and fragile nails, skin rash, garlic-like breath and skin odor, fatigue, irritability, hyperreflexia, rhabdomyolysis, interstitial nephritis, anemia, thrombocytopenia, hemolysis, renal failure, weight loss

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid.

Treatment

The treatment consists of its withdrawal and symptomatic treatment, if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

COBADEX CZS contains active substances with synergistic and therapeutic actions, necessary for maintenance and/or improvement of functional activities of the body.

Vitamins and minerals are included to treat deficiencies occurred. Many of those act as co-factors for various metabolic functions.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Multivitamins and other minerals, including combinations; ATC Code: A11AA03.

Pharmacodynamic Effects

Vitamin B_6 (Pyridoxine hydrochloride)

It takes part in formation of some important co-enzymes involved in protein metabolism and HEM biosynthesis. As a coenzyme it functions in metabolism of amino acids, glycogen and sphingoid bases.

Nicotinamide

Nicotinamide is involved in a large number of processes such as production of energy, synthesis of fatty acids, cholesterol, steroids, signal transduction and the maintenance of integrity of genome.

Vitamin B_{12} (Cyanocobalamin)

It is essential for erythropoiesis, formation of myelin sheet and synthesis of the DNA.

Folic acid

It is essential for erythropoiesis, maturation of red blood cells and biosynthesis of the DNA.

Chromium

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism.

Selenium

Selenium has been implicated in the protection of body tissues against oxidative stress, maintenance of defences against infection, modulation of growth and development. It acts as an antioxidant and is essential for glutathione peroxidase.

Zinc

Zinc is an essential component of a large number (> 300) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients. Zinc plays a major role in the immune system. It also acts as an antioxidant. It is important for normal growth, wound healing and sexual maturation, for crystallization and release of insulin (the pancreas of diabetic individuals contains only half of the normal quantity of zinc).

5.3 Pharmacokinetic Properties

There are no relevant data available.

6. NON-CLINICAL PROPERTIES

There are no relevant data available.

7. DESCRIPTION

Film Coated Tablet

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8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Blister strip of Tablets packed in carton.

8.4 Storage and Handling Information

Store at temperature not exceeding 30^0 C. Protect from direct sunlight.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *COBADEX CZS*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

20-FEB-2024

Version: CBD-CZS/PI/IN/2024/01

Adapted from:

- *Theragran M NCDS v05 dated 21-Jan-2020.*
- *Theragran Stress NCDS v04 dated 16-Dec-2019.*
- *PDR for Nutritional Supplement 2nd ed.*