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

COBADEX - Z CAPSULES

1. GENERIC NAME

Vitamin B_{12} - B Complex with Vitamin C and Zinc Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:	
Thiamine Mononitrate IP	10 mg
Vitamin B_2 IP	10 mg
Vitamin B_6 IP	3 mg
Nicotinamide IP	100 mg
Calcium Pantothenate IP	50 mg
Folic Acid IP	1500 mcg
Vitamin B_{12} IP	15 mcg
Vitamin C IP	150 mg
Zinc Sulphate Monohydrate IP (equivalent to 15 mg of elemental zinc)	41.4 mg
Biotin USP (Appropriate overages added)	100 mcg

Colours: Brilliant Blue FCF, Carmoisine, Tartrazine, Ferric Oxide USPNF (Yellow) and Titanium Dioxide IP in empty capsule shells

3. DOSAGE FORM AND STRENGTH

Capsules for oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

COBADEX - Z CAPSULES is indicated for the treatment of vitamin B-complex, vitamin C and zinc deficiency states in adults which may be associated with the following conditions:

- Dietary restrictions: in conditions such as obesity, cardiovascular diseases, chronic diarrhoea or dysentery, diabetes mellitus etc.
- Malnutrition
- Infections or recovering from infections
- Long term antibiotic use

4.2 Posology and Method of Administration

Route of Administration

For oral use.

Adults

One capsule once daily.

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

Children

COBADEX - Z CAPSULES is not recommended for paediatric use.

Elderly

There are no relevant data available.

Renal Impairment

Caution should be exercised when administering *COBADEX - Z CAPSULES* to patients with renal disorders

Hepatic Impairment

Caution should be exercised when administering *COBADEX - Z CAPSULES* to patients with hepatic disorders

4.3 Contraindications

COBADEX - Z CAPSULES is contraindicated in:

- Hypersensitivity to any of the components.

4.4 Special Warnings and Precautions for Use

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.

Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely-elevated or false-negative test results may be obtained from plasma, faeces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used.

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

Tolerance

Tolerance may be induced with prolonged use of large doses of vitamin C, resulting in symptoms of deficiency when intake is reduced to normal.

Others

High dose of nicotinamide should be used with caution in patients with peptic ulcer disease, gastritis, liver disease, gall bladder disease, diabetes and gout.

4.5 Drug Interactions

Antibiotics

COBADEX - Z CAPSULES decreases the absorption of some fluoroquinolones, tetracyclines and penicillamine derivatives, therefore doses should be separated by at least 3 hours.

Tetracycline antibiotics also decrease zinc absorption, they should therefore be administered 2 hours before or 3 hours after the administration of zinc, 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}.

Concomitant use of zinc and quinolones may decrease the absorption of both zinc and the quinolone.

Acetylsalicylic acid

Aspirin might reduce the absorption of ascorbic acid by about one-third. Serum salicylate levels do not appear to be affected by ascorbic acid.

Folic acid antagonists

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

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.

Iron chelators

High-dose vitamin C may cause cardiac disorders in some patients given desferrioxamine (deferoxamine). Other iron chelators are expected to interact similarly.

Oral contraceptives

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

Large supplements of vitamin C have been reported to increase serum ethinylestradiol concentrations in women taking oral contraceptives, but a further study showed no effect on either ethinylestradiol or levonorgestrel.

Levodopa

COBADEX - Z CAPSULES 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 - Z CAPSULES contains vitamin B_6 which reduces the activity of altretamine.

Antiepileptics

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

Antiepileptics may produce folate deficiency states.

Serum levels of anticonvulsant drugs may be reduced by the co-administration of folate e.g. folic acid possibly reduces the plasma concentration of phenobarbital, phenytoin and primidone

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

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} and dietary vitamin C.

Aluminium-containing antacids

COBADEX - Z CAPSULES contains ascorbic acid, which may increase gastrointestinal absorption of aluminium. Concomitant administration of aluminium-containing antacids may affect urinary aluminium elimination. Concurrent administration of antacids and ascorbic acid is not recommended, especially in patients with renal insufficiency.

Phosphates

Phosphorus-containing preparations may reduce the absorption of zinc.

Iron supplements

The absorption of zinc may be reduced by additionally taken iron supplements.

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.

Vitamin C

As *COBADEX - Z CAPSULES* contains vitamin C, it may increase the absorption of iron from the gastrointestinal tract. This should be borne in mind in the case of additional iron supplementation

Alcohol

Alcohol may produce folate deficiency states.

Fluoride

As *COBADEX - Z CAPSULES* contains calcium (as calcium pantothenate), it reduces the absorption of fluoride, therefore doses should be separated by at least 3 hours.

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.

Caffeine

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

Oxalic acid/Phytic acid

Concomitant intake of foods rich in oxalic acid (spinach, sweet potatoes, and beans, etc.) or phytic acid (raw beans, seeds, nuts and grains, and soy isolates) may decrease the absorption of zinc.

Tea

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

Raltitrexed

Concomitant use of folic acid with raltitrexed should be avoided.

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

Fertility

There are no relevant data available.

Pregnancy

COBADEX - Z CAPSULES should be administered to pregnant women only after consultation with a physician.

Lactation

COBADEX - Z CAPSULES 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 - Z CAPSULES* 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 - Z CAPSULES*. The frequency of these events cannot be estimated from the available data.

Immune system disorders

Hypersensitivity reactions, urticaria, rash, pruritus, Anaphylactic reactions.

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, gastrointestinal discomfort, metallic taste

Nervous system disorders

Headache, dizziness, precipitation, exacerbation or prolongation of neurological signs and symptoms of vitamin B_{12} deficiency due to folic acid, drowsiness

Skin and subcutaneous tissue disorders

Photosensitivity

Renal and urinary disorders

Yellow orange discoloration to urine, hyperoxaluria

Metabolic disorders

Diabetogenic effects

4.9 Overdose

Overdose of *COBADEX - Z CAPSULES* can lead to the following symptoms and signs.

Symptoms and signs

Diarrhoea, polyuria, sensory neuropathy, peripheral neuropathy, nausea, vomiting, abdominal pain, abdominal cramps, flatulent distension, gastrointestinal obstruction, esophagitis, loss of appetite, breast soreness, photosensitivity, elevations in liver tests and liver damage, including jaundice and parenchymal liver cell injury, headache, dizziness, sleep disturbances, mental changes, other gastrointestinal effects, hyperoxaluria with or without renal failure, formation of renal calcium oxalate calculi. There is a risk of haemolysis if high doses of ascorbic acid are taken.

Decreased HDL has been reported with high doses of zinc. High dose of zinc can be immunosuppressive. Chronic intake of high doses of zinc can lead to copper deficiency.

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. Further management should be as clinically indicated

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action and Pharmacodynamic Effects

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

Vitamins, their precursors and mineral (zinc) are included to treat deficiencies occurred. Many of those act as co-factors for various metabolic functions.

Biotin (Vitamin H)

It is involved in carbohydrate and fat metabolism.

Folic acid

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

Pantothenic acid

It is a precursor of co-enzyme A, necessary for energy production, involved in fatty acid metabolism, formation of acetylcholine and improvement of epithelization and wound healing. It is also necessary for folic acid and carbohydrates metabolism.

Vitamin B_1 (Thiamine Mononitrate)

Vitamin B_1 is an essential co-enzyme in oxidative metabolism of α-ketoacids and increases the activity of acetylcholine in nerve endings.

Vitamin B_2 (Riboflavin)

Vitamin B_2 is an essential component in function of certain co-enzymes important for energy production taking part in numerous oxidation and reduction reactions. It has also an important role in maintaining a healthy skin.

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.

Vitamin C (Ascorbic acid)

Vitamin C is an electron donor (reducing agent or antioxidant) for 11 enzymes. It has a role in hydroxylation of certain compounds. It helps in maintenance of intracellular skeleton of cartilages, bones and teeth. It is essential in maintenance of capillary wall integrity and regulation of capillary permeability. Vitamin C promotes absorption of soluble non-haem iron.

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).

5.2 Pharmacodynamic Properties

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

5.3 Pharmacokinetic Properties

There are no relevant data available.

6. NONCLINICAL PROPERTIES

There are no relevant data available.

7. DESCRIPTION

Capsules for oral administration

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8. PHARMACEUTICAL PARTICULARS

List of Excipients

Paraffin liquid, lactose, magnesium stearate, gelatin triturate (cyanacobalamin) and colloidal silicon dioxide.

Empty hard gelatin size '1' locking type capsules with brown cap and yellow body containing gelatin, purified water, methyl paraben, propyl paraben, brilliant blue FCF, carmoisine, tartrazine, ferric oxide (yellow) and titanium dioxide.

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

Aluminium strips in a carton.

8.4 Storage and Handling Information

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

There are no special requirements for use or handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *COBADEX - Z CAPSULES*. Patients 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 LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

12-MAR-2020

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Adapted from:

- *Theragran Stress NCDS v04 dated 16 December 2019*
- *Theragran H NCDS v04 dated 23 November 2018*
- *PDR for Nutritional Supplement 2nd ed.*