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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Calcium with Vitamin D_3 and Minerals Tablets

(Brand Name: VEBA®-PLUS Tablets)

2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Calcium Citrate Malate USP …….. 1200 mg.

equivalent to elemental Calcium …… 250 mg.

Vitamin D_3 (Stabilized) equivalent to Vitamin D_3 IP …… 200 I.U.

Magnesium Hydroxide IP equivalent to elemental Magnesium … 25 mg.

Sodium Borate USNF equivalent to elemental Boron ……... 0.5 mg.

Manganese Sulfate USP equivalent to elemental Manganese …… 2.5 mg.

Zinc Sulphate IP equivalent to elemental Zinc …….. 7.5 mg.

Copper Sulphate BP equivalent to elemental Copper …… 0.75 mg.

Colour: Titanium Dioxide IP

Appropriate overages of Vitamin D_3 added

3. Dosage Form and Strength

Dosage Form: Tablet.

Dosage Strength: Calcium 250 mg, Vitamin D_3 200 IU, Magnesium 25 mg, Boron 0.5 mg, Manganese 2.5 mg, Zinc 7.5 mg, Copper 0.75 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

VEBA-PLUS Tablets are indicated in the following conditions:

- As a supplementary source of calcium when normal body requirements are high e.g. in pregnancy, lactation, or postmenopausal women.
- It is also prescribed for certain bone-related conditions like osteoporosis.
- Prevention and treatment of calcium deficiency in adults.

4.2Posology and Method of Administration

For oral administration.

Adults and adolescents: 1 to 2 tablets to be administered twice daily. The tablet should be swallowed whole with water.
Or, as prescribed by the physician.

4.3Contraindications

VEBA-PLUS Tablets are contraindicated in the following:

- In patients with known hypersensitivity to any component of the product.
- In patients with hypercalcemia and hypercalciuria.
- Disease and/or conditions such as primary hyperparathyroidism, myeloma, bone metastases which results in hypercalcaemia and/or hypercalciuria.
- In patients with evidence of vitamin D toxicity (hypervitaminosis D).
- Nephrocalcinosis, nephrolithiasis.
- Severe renal impairment and renal failure.
- Cardiac diseases like ventricular fibrillation.

4.4Special Warnings and Precautions for Use

Hypercalcaemia: Daily intake of calcium above 2000 mg has been associated with an increased risk of adverse effects, including hypercalcemia and kidney stones. In patients with a history of kidney stones or hypercalciuria, metabolic assessment to be done to find out treatable causes of these conditions. If administration of calcium is needed in these patients, urinary calcium excretion and other appropriate testing should be undertaken periodically.
Long term use: During long-term treatment, serum calcium levels and renal function (serum creatinine levels) should be monitored. Monitoring is especially important in patients on concomitant treatment with cardiac glycosides or thiazide diuretics and in patients with a high tendency to calculus formation. In case of hypercalcaemia or signs of impaired renal function the dose should be reduced or the treatment discontinued.
Sarcoidosis: Calcium preparations should be administered with caution to patients suffering from sarcoidosis, due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.
Immobilised patients with osteoporosis: Calcium preparations should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.
Renal impairment: Vitamin D should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. Patients with renal impairment are at potential risk of hyperphosphaetemia, nephrolithiasis, and nephrocalcinosis. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and other forms of vitamin D should be used.
Other products containing calcium or vitamin D: While prescribing other medicinal products containing calcium and/or vitamin D, quantities of these agents should be considered to avoid overdosage. If required, additional doses of calcium or vitamin D should be taken under close

medical supervision. In such cases, it is necessary to monitor serum calcium levels and urinary calcium excretion frequently. Calcium and vitamin D intake from other sources (food, dietary supplements) should also be estimated, before administration of this product.

Tetracyclines or quinolones: Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with caution.

4.5Drug Interactions

Thiazide diuretics: Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Corticosteroids: Calcium absorption is reduced in patients receiving systemic corticosteroid therapy. During concomitant use, it may be necessary to increase the dose of calcium.

Ion exchange resins, liquid paraffin: Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. Therefore a time interval as long as possible between the intakes should be recommended.

Phenytoin, barbiturates: Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D_3 as these agents increases metabolism of vitamin D_3.

Digoxin/cardiac glycosides: Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and vitamin D. Thus, hypercalcemia must be avoided in patients on digitalis therapy. Strict medical supervision and if necessary, monitoring of electrocardiogram (ECG) and serum calcium levels is needed.

Levothyroxine, bisphosphonates, sodium fluoride, quinolones, tetracyclines, iron: If calcium and any of these agents used concomitantly, calcium reduces absorption of these agents; thus, efficacy of these agents may be reduced. Therefore, it is advisable that administration of calcium and any of these agents should be separated by at least 2 to 4 hours.

Oxalic acid, phytic acid: Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

Orlistat: Treatment with orlistat may potentially impair the absorption of fat-soluble vitamin such as vitamin D_3.

4.6Use in Special Populations

Pregnant Women

VEBA-PLUS Tablets can be administered safely during pregnancy. In pregnancy, demand for calcium and other micronutrients increases remarkably and thus, supplementation is essential. Studies in animals have shown reproductive toxicity of high doses of vitamin D. Thus, in pregnant women, overdoses of calcium and vitamin D should be avoided, as permanent hypercalcemia has been related to adverse effects on developing fetus.

Lactating Women
VEBA-PLUS Tables are recommended for use during lactation. Calcium passes slightly into breast-milk, without having a negative effect on children. Vitamin D and its metabolites also pass into breast-milk. This should be considered when giving additional vitamin D to the infant/child.

Paediatric Patients
VEBA-PLUS Tablets are not intended for use in paediatric population. Children should use other paediatric formulations appropriate for their age group.

Geriatric Patients
Generally, dose adjustment is not required in the geriatric population. Elderly patients with normal renal and hepatic function may be given the same dose as recommended for adults.

Renal Impairment Patients
VEBA-PLUS Tablets should not be used in patients with severe renal impairment. Further, use in patients with renal failure is contraindicated. VEBA-PLUS Tablets should be used with caution in patients with mild to moderate renal impairment and the effect on calcium and phosphate levels should be monitored. Patients with renal impairment are at potential risk of hyperphosphatemia, nephrolithiasis and nephrocalcinosis. The risk of soft tissue calcification should also be considered in such patients.

4.7Effect on Ability to Drive and Use Machines
VEBA-PLUs Tablets are not expected to have any influence on the ability to drive and use machines.

4.8Undesirable Effects
Gastrointestinal disorders: Nausea, vomiting, diarrhea, abdominal pain, constipation, flatulence, and abdominal distension may occur with the use of calcium preparations.
Immune system disorders: Hypersensitivity reactions, anaphylactic reaction.
Metabolism and nutrition disorders: Hypercalcaemia, hypercalciuria. Patients with tertiary hyperparathyroidism, renal failure, or on regular haemodialysis are particularly more prone to develop hypercalcemia.
Respiratory, thoracic and mediastinal disorders: Laryngeal oedema.
Skin and subcutaneous tissue disorders: Rash, pruritus, urticaria, angioedema.

4.9Overdose
Symptoms: Overdose of calcium with vitamin D causes gastro-intestinal disturbances and hypercalcemia. Acute symptoms of calcium and vitamin D intoxication are anorexia, headache,

vomiting, and constipation. Chronic symptoms may include weakness, loss of weight, sensory disturbances, fever, thirst, polyuria, dehydration, apathy, and arrested growth. Urinary tract infections may occur. There are potential, but rare risks of metastatic calcification of the renal cortex, myocardium, lungs and pancreas; and alkalosis.

Treatment: Treatment of hypercalcemia should be aimed at lowering serum calcium levels through a high fluid intake and low calcium diet. Treatment should consist of general supportive measures. Induction of emesis or gastric lavage may be of benefit to prevent further absorption. Administration of liquid paraffin may be useful to promote fecal excretion. Serum electrolyte determinations (especially calcium), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. In severe cases, treatment with corticosteroids may be necessary.

5. Pharmacological Properties

5.1 Mechanism of Action

Calcium, vitamin D_3 and other micronutrients/minerals are vital for bone health in all age groups. This is even more so in children, pregnancy, lactation, and in elderly population. Calcium is core element required for bone formation as well as its strengthening. The growth of the skeleton requires a positive calcium balance. Vitamin D helps absorption of calcium from gut, deposition of the same into the bones (bone mineralization) and also favors re-absorption from the kidneys. Thus, it helps to maintain positive calcium balance. Supplementation of calcium, vitamin D, and minerals such as magnesium, boron, manganese, zinc, and copper are essential for maintaining strong and healthy bones. Need of such supplementation is higher in special population such as in pregnant women, lactating women, geriatric people etc. Further, calcium and mineral supplementation is also useful for prevention and treatment of bone related disorders such osteopenia and osteoporosis.

5.2Pharmacodynamic Properties

Calcium Citrate Malate – CCM

Nearly about 99% of total body calcium is located in the skeleton. The remaining 1% is equally distributed between the teeth and soft tissues, with only 0.1% in the extracellular fluid (ECF). In the skeleton it constitutes 25% of the dry weight. Calcium provides rigidity to the skeleton. Calcium ions play a role in many metabolic processes. Calcium is essential, both during pregnancy and lactation, for proper formation of bones and teeth of the offspring, for secretion of breast milk rich in calcium and to prevent osteoporosis in the mother. Administration of calcium and vitamin D_3 counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which cause increased bone resorption.

Vitamin D_3

Vitamin D is required to maintain normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralization of bone, muscle contraction, nerve conduction, and

general cellular function in all cells of the body. Active form of vitamin D (calcitriol) regulates the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins. Vitamin D also modulates the transcription of cell cycle proteins, which decrease cell proliferation and increase cell differentiation of a number of specialized cells of the body (e.g., osteoclastic precursors, enterocytes, and keratinocytes). This property of vitamin D demonstrates its actions in bone resorption, intestinal calcium transport, and in skin.

Magnesium

Magnesium is involved in the bone formation. It guards against the bone loss, bone breaks, and the bone-thinning disease, osteoporosis. Magnesium affects levels of calcitonin and parathyroid hormone (PTH) and helps convert vitamin D to active form, which are responsible for maintaining the calcium hemostasis and bone health. Adequate magnesium intake is associated with higher bone density.

Boron

Boron or boric acid is shown to be an essential ultra-micronutrient in human beings. Boron exists as boric acid in dilute solutions at pH of blood 7.4. Boric acid forms ester complexes with hydroxyl groups of organic compounds. Boron has a role in cell membrane function or stability such that it influences the response to hormone action, transmembrane signaling or transmembrane movement of regulatory ions. Boron stabilizes and extends the half-life of vitamin D and estrogen.

Manganese

Manganese is the preferred cofactor of enzymes called glycosyl transferases; these enzymes are required for the synthesis of proteoglycans that are needed for the formation of healthy cartilage and bone.

Zinc

Zinc is an essential trace element required for all forms of life. It is a cofactor in many metalloenzymes and is an extremely important element for bone health; skeleton contains a large proportion of the total body burden of zinc. It plays a pivotal role in the regulation of bone homeostasis. Many zinc-related proteins are found to involve in the regulation of cellular function in osteoblasts and osteoclasts. Zinc stimulates cell differentiation, cell proliferation, and mineralization in osteoblasts through gene expression of various proteins including type I collagen, alkaline phosphatase, and osteocalcin. Furthermore, zinc inhibits osteoclastic bone resorption suppressing osteoclast-like cell formation, inhibits action of receptor activator of nuclear factor kappa-B ligand (RANKL) in pre-osteoclasts and stimulates gene expression of osteoprotegerin (OPG) in osteoblastic cells. Adequate levels of zinc are necessary to form collagen tissue, unite bone fractures, heal wounds and prevent osteoporosis.

Copper

Copper aids in the development of red blood cells as well as the maintenance of healthy bones, nerves and the immune system. Copper is an essential mineral, primarily found in the bloodstream, as a cofactor to many enzymes. As a general enzymatic cofactor, it actives lysil oxidase which induces the formation of lysine crosslinks in collagen and elastin which are required for formation of strong, flexible elastic tissue, removes bone free radicals as a cofactor of antioxidant enzymes, directly inhibits osteoclastic resorption playing an important role in bone formation and mineralization.

5.3Pharmacokinetic Properties

Calcium Citrate Malate - CCM

Calcium is absorbed from small intestine in ionic form by both active and passive mechanisms. Calcium absorption from calcium citrate malate is consistently 36% (27 to 53%). Overall, results from human and animal studies show that calcium from calcium citrate malate is more bioavailable (8 to 15%) than calcium from other calcium sources. Citrate and malate anions chelated to calcium in calcium citrate malate are considered to enhance calcium absorption, possibly by forming relatively stable soluble complexes, such that precipitation of calcium by phosphate in the gut is not chemically favored and the likelihood of calcium absorption is improved. Thus, calcium citrate malate can be absorbed even in the absence of gastric acid (achlorhydria).

Active mechanism for calcium absorption depends on the action of the active form of vitamin D, 1,25-dihydroxycholecalciferol. Calcium that is unabsorbed from intestine is excreted in feces. Greater than 98% of calcium from glomerular filtrate is reabsorbed. Approximately 40% of calcium in the plasma is bound to proteins, primarily albumin; about 50% of calcium in the plasma is diffusible ionic calcium and about 10% is diffusible, but it is complexed with anions such as phosphate and citrate.

Vitamin D_3

About 50 to 80% of the ingested vitamin D is absorbed in the small intestine. It is carried to the blood stream by lymphatics and it binds to alpha-globulin vitamin D in the blood. A large fraction of the circulating vitamin D is extracted by the hepatocytes and converted to 25-hydroxy vitamin D (25(OH)D) with the help of the enzyme, 25-hydroxylase. The 25(OH)D is the major circulating form of vitamin D and it is actively converted to 1,25-dihydroxyvitamin D in the kidneys by the enzyme 1,25-hydroxyvitamin D_1-alphahydroxylase. Deactivation of 1,25-dihydroxyvitamin D and 25(OH)D occurs by CYP24. Vitamin D and its metabolites are primarily excreted via the biliary root. The final degradation product of 1,25-dihydroxyvitamin D is calcitroic acid, which is excreted by the kidneys.

Magnesium

About 15 to 50% of magnesium hydroxide is absorbed as magnesium ions very slowly through the small intestine. Magnesium hydroxide does not have any protein binding properties. It does not undergo any metabolism. Magnesium is rapidly excreted in the urine through the kidneys. The unabsorbed drug is mainly excreted in the feces and saliva.

Boron

Sodium borate is rapidly absorbed, with more than 90% of the ingested boron being absorbed and transported as boric acid. This is the normal hydrolysis end product of most boron compounds at the pH of the gastrointestinal tract. Boron is distributed throughout the tissues and organs. There is lack of accumulation of boron in tissues and relatively narrow range of boron concentrates in the blood. Absorbed boron is rapidly excreted in the form of urine.

Manganese

The absorption of manganese occurs from the small intestine. A fraction of manganese is oxidized to Mn^{+3} and is bound to plasma protein transferrin. Transferrin-bound manganese is rapidly taken up by the extra-hepatic tissues. Within the cells, manganese is predominantly concentrated in the mitochondria. Manganese is totally removed in the feces; trace amounts are excreted in the urine.

Zinc

Zinc is absorbed up to 10 to 40% primarily by the ileum part of the small intestine. Phytates and fiber reduces zinc absorption. Iron also affects zinc absorption. Glucose, lactose and soy protein enhances zinc absorption. Albumin is the major transport for zinc. Other proteins like transferrin, ceruloplasmin and gamma-globulin also bind significant amount of zinc. A small fraction exists mostly bound to amino acids and a still smaller fraction exists as ionic zinc. Zinc is almost solely excreted via feces in healthy individuals. Only 0.5 mg of zinc per day is excreted in the urine.

Copper

Copper is absorbed from the small intestine by an active saturable mechanism. The absorbed copper quickly disappears from the plasma; most is taken up by the liver and some by the kidneys. Copper bound to ceruloplasmin is released from the liver into the blood for transport to other cells and tissues. Copper is totally removed in the feces; trace amounts are excreted in the urine.

6. Nonclinical Properties

6.1 Animal Toxicology

For vitamin D3, at doses far higher than the human therapeutic range, teratogenicity has been observed in animal studies. There is further no relevant information available for other ingredients.

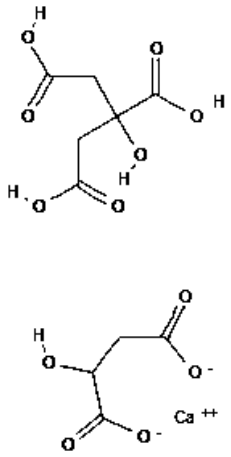
7. Description

VEBA-PLUS Tablet are off white with green tint coloured, Capsule shaped with breakline on one side & plain on other side film coated tablets.

VEBA-PLUS Tablets contain 250 mg of calcium, 200 IU of vitamin D_3, 25 mg of magnesium, 0.5 mg of boron, 2.5 mg of manganese, 7.5 mg of zinc, and 0.75 mg of copper for oral administration in adults and adolescents.

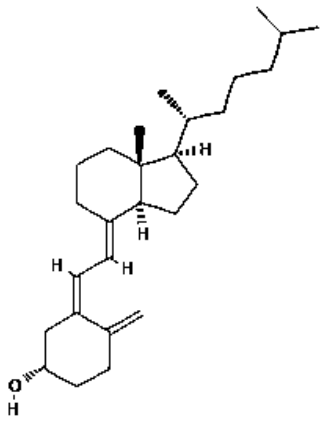
Calcium Citrate Malate

Molecular Weight: 364.27 g/mol.
Molecular Formula: C10H12CaO12.
Chemical Name: Calcium; 2-hydroxybutanedioate;2-hydroxypropane-1,2,3-tricarboxylic acid.
Structural Formula:



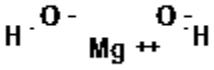
Vitamin D_3

Vitamin D_3 appears as fine colorless crystals.
Molecular Weight: 384.6 g/mol.
Molecular Formula: C27H44O.
Chemical Name: (1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol.
Structural Formula:



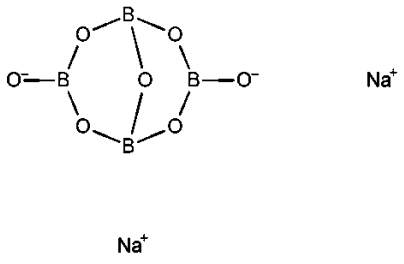
Magnesium Hydroxide

Magnesium hydroxide is odourless, white bulky, amorphus powder.
Molecular Formula: H2MgO2.
Molecular Weight: 58.32 g/mol.
Chemical Name: Magnesium;dihydroxide.
Structural Formula:



Sodium Borate

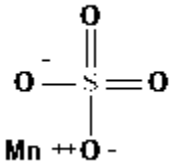
Molecular Weight: 201.22 g/mol.
Molecular Formula: B4Na2O7.
Chemical Name: disodium; [oxido(oxoboranyloxy)boranyl]oxy oxoboranyloxyborinate; decahydrate.
Structural Formula:



Manganese Sulfate

Molecular Formula: MnSO4.
Molecular Weight: 151 g/mol.
Chemical Name: Manganese(2+);sulfate.

Structural Formula:



Zinc Sulphate

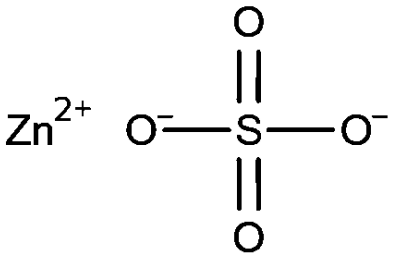
Anhydrous zinc sulphate is a colorless crystalline solid which is soluble in water. Zinc sulphate is also obtained as a hexahydrate and as a heptahydrate.

Molecular Formula: ZnSO4.

Molecular Weight: 161.4 g/mol.

Chemical Name: Zinc(2+);sulphate.

Structural Formula:



Copper Sulphate

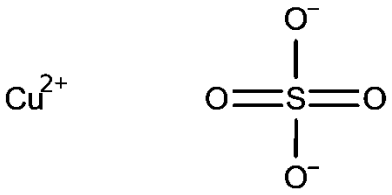
Cupric sulphate appears as a white or off-white solid white is very soluble in hot water and soluble cold water.

Molecular Formula: CuSO4.

Molecular Weight: 159.61 g/mol.

Chemical Name: Copper(2+);sulphate.

Structural Formula:



Inactive ingredients (excipients) of VEBA-PLUS Tablet contains Starch, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Talcum, Magnesium Stearate & Instacoat Aqua III White.

8. Pharmaceutical Particulars

8.1 Incompatibilities
None known.

8.2 Shelf-life
18 months.

8.3 Packaging Information
15 tablets per Blister.

8.4 Storage and Handling Instructions
Store below 25°C in a dry place.
Keep out of reach of children.

9. Patient Counseling Information
Administration Instructions

- Instruct patients to take prescribed dose of VEBA-PLUS Tablets as directed.
- Instruct patients not to use this medicine in case of severe renal impairment, renal failure, and during vitamin D toxicity (hypervitaminosis D).
- Instruct patients to avoid taking calcium products within two hours of eating foods high in oxalate (green leafy vegetables, spinach, rhubrb) and phytate (seeds, legumes, nuts, whole cereals) because of decreased absorption.
- If required, other preparations containing calcium and/or vitamin D can be taken under medical supervision just to avoid overdosage.

10.Details of Manufacturer
Akums Drug & Pharmaceuticals Ltd.
At: Plot No 26A,27-30, Sector-8A, I.I.E.,SIDCUL,
Ranipur, Haridwar – 249403, Uttarkhand.

11.Details of Permission or License Number with Date
Manufacturing license No.:8/UA/LL/SC/P-2014. Date of Product Permission: 31/10/2018

12. Date of Revision
November 2022.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.