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

Cholecalciferol Granules
(Brand Name: BLUVIT®-D_3 Sachet)

2. Qualitative and Quantitative Composition

Each sachet of 1gram contains:
Cholecalciferol IP …….. 60,000 IU.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Granules for oral use.
Dosage Strength: Cholecalciferol 60,000 IU per sachet.

4. Clinical Particulars

4.1 Therapeutic Indication

BLUVIT-D_3 Sachet is indicated for treatment and prevention of vitamin D deficiency or insufficiency.

4.2Posology and Method of Administration

For oral administration in children and adults.
Loading Dose: One BLUVIT-D_3 Sachet (Cholecalciferol 60,000 IU) to be given once weekly for 6 to 8 weeks to restore serum 25(OH)D level to normal i.e., 30 ng/ml.
Maintenance Dose: To sustain serum 25(OH)D sufficiency, a daily maintenance dose of cholecalciferol (400 to 2000 IU/day) is required. However, a high dose of cholecalciferol (60,000 IU) was found to be effective when given on monthly basis. Thus, to improve patient compliance and adherence to the therapy, one BLUVIT-D_3 Sachet may be given every month as required. Follow-up 25(OH)D measurements should be made 3 to 4 months after initiating maintenance therapy to confirm that the target level has been achieved. Certain population is at high risk of vitamin D_3 deficiency, and may require higher doses and frequent monitoring of serum 25(OH)D. Or, as prescribed by the physician.

Method of Administration

Pour the contents of the sachet into a glass of non-carbonated water. Shake/stir the contents until the granules have been dispersed. Drink it immediately.
Vitamin D_3 is well absorbed from the gastro-intestinal tract in the presence of bile. Therefore, a BLUVIT-D_3 Sachet is to be administered preferably with the main meal of the day (it is best to take this preparation after a meal, but, it can be administered with or without food).

4.3Contraindications

BLUVIT-D_3 Sachets are contraindicated in the following:

- Hypersensitivity to cholecalciferol (vitamin D) or to any excipient of the formulation.
- Hypervitaminosis D.
- Nephrolithiasis.
- Diseases or conditions resulting in hypercalcemia and/or hypercalciuria.
- Renal osteodystrophy with hyperphosphataemia.
- Severe renal impairment.

4.4Special Warnings and Precautions for Use

During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with a high tendency for developing renal calculi. Treatment must be reduced or suspended if urinary calcium exceeds 300 mg/24 hours. In case of hypercalcaemia or signs of impaired renal function, treatment with cholecalciferol should be discontinued.
The dose of cholecalciferol should be considered when prescribing other drugs containing vitamin D. 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.
Cholecalciferol should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.
Cholecalciferol should be used with caution in immobilized patients with osteoporosis due to the increased risk of hypercalcaemia. The cholecalciferol treatment should be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.
Conditions like arteriosclerosis or cardiac function impairment may be exacerbated due to the possibility of hypercalcaemia and elevated serum cholesterol concentrations.
Cholecalciferol should be administered with caution in patients with hyperlipidaemia as it could potentially exacerbate low-density lipoprotein (LDL) elevation. Administration of cholecalciferol in patients with hyperphosphataemia may put the patient at risk for metastatic calcification; normalization of phosphate levels are indicated prior to therapy.

4.5Drug Interactions

Cholestyramine/Orlistat: Since vitamin D is fat-soluble, it is expected that mineral oils, orlistat, and bile acid sequestrants (e.g., cholestyramine, colestipol) may reduce intestinal absorption of vitamin D. Hence, these drugs should be taken several hours apart.

Phenytoin/Phenobarbital: The co-administration of phenytoin or phenobarbital will not affect plasma concentrations of vitamin D, but may reduce endogenous plasma levels of calcitriol by accelerating metabolism. Since the blood level of calcitriol will be reduced, higher doses of cholecalciferol may be necessary if these drugs are administered simultaneously.

Thiazides: Thiazides are known to induce hypercalcaemia by the reduction of calcium excretion in urine. Some reports have shown that the concomitant administration of thiazides with vitamin D causes hypercalcaemia. Therefore, precaution should be taken when co-administration is necessary.

Digitalis: Vitamin D dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.

Ketoconazole: Ketoconazole may inhibit both the synthetic and catabolic enzymes of vitamin D. Reductions in serum endogenous vitamin D concentrations have been observed following the administration of 300 mg/day to 1200 mg/day ketoconazole for a week to healthy men. However, *in vivo* drug interaction studies of ketoconazole with vitamin D have not been investigated.

Corticosteroids: A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit calcium absorption.

Phosphate-Binding Agents: Since vitamin D also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration.

Calcium Supplements: Uncontrolled intake of additional calcium-containing preparations should be avoided.

Magnesium: Magnesium-containing preparations (e.g., antacids) may cause hypermagnesaemia and should, therefore, not be taken during therapy with vitamin D by patients on long-term renal dialysis.

4.6Use in Special Populations

Pregnant Women

There is limited amount of data regarding use of a higher dosage of cholecalciferol in pregnant women. Studies in animals have shown reproductive toxicity. The usually recommended intake for pregnant women is 400 to 600 IU daily. However, in women who are considered to be vitamin D deficient, a higher dose may be required. As per the reports, vitamin D supplementation of 4000 IU/day is safe and effective in achieving serum 25(OH)D sufficiency in all pregnant women and their neonates. Thus, due to its higher dosage strength, BLUVIT-D_3 Sachets are not recommended for use during pregnancy.

Lactating Women

Cholecalciferol and some of its active metabolites pass into breast milk. The recommended daily regimen of vitamin D for breast feeding women is 600 IU. However, in vitamin D deficiency states, lactating women may need to take 1400 to 1500 IU of cholecalciferol per day. Also, to satisfy their infant's requirement, nursing mothers may need to take 4000 to 6000 IU of cholecalciferol per day, if they choose not to give a vitamin D supplement to their infant. Thus, due to its higher dosage strength, BLUVIT-D_3 Sachets are not recommended for use in lactating women.

Paediatric Patients
BLUVIT-D_3 Sachets can be safely administered to children. Dosage is the same as for adults.

Geriatric Patients
Elderly patients may be given the same dose as recommended for adults. However, studies have shown that the elderly people may have greater requirement for vitamin D due to a possible decrease in the capacity of skin to produce pro-vitamin D_3, or a decrease in exposure to the sun, or impaired renal function, or impaired vitamin D absorption.

Renal Impairment Patients
Cholecalciferol should be used with caution in patients with renal impairment and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal impairment, vitamin D in the form of cholecalciferol is not metabolized normally and another form of vitamin D should be used. Use of cholecalciferol is contraindicated in patients with severe renal impairment.

Hepatic Impairment Patients
In patients with liver dysfunction, absorption of cholecalciferol may be impaired. Thus, cholecalciferol should be used with caution in patients with hepatic impairment.

4.7Effect on Ability to Drive and Use Machines
There are no data on the effects of cholecalciferol (Vitamin D_3) on the ability to drive or use machines. However, this effect is unlikely to occur.

4.8Undesirable Effects
Vitamin D at normal doses does not cause any side effects. However, side effects which have been reported with the use of vitamin D have included arrhythmias, confusion, dry mouth, headache, lethargy, metallic taste, muscle or bone pain, sluggishness, nausea, vomiting, constipation, loss of appetite, increased thirst, increased urination, and mental/mood changes.
Pruritus, rash, and urticaria may occur rarely with the use of cholecalciferol. A very serious allergic reaction to cholecalciferol is rare. However, medical help may be required in case of a serious

allergic reaction, including rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, and trouble breathing.

Prolonged consumption of vitamin D may lead to hypercalcemia, hypercalciuria, and hyperphosphatemia, symptoms of which may include:

Symptoms of hypercalcemia: Constipation, nausea, decreased appetite, abdominal pain, peptic ulcers, kidney stones, flank pain, frequent urination, confusion, dementia, memory loss, depression, bone pain, fractures, curving of the spine, and loss of height.

Symptoms of hypercalciuria: Dysuria, abdominal pain, irritability, urinary frequency, urinary urgency, change of urinary appearance, colic, daytime incontinence, isolated or recurrent urinary tract infections, vesicourethral reflux.

Symptoms of hyperphosphatemia: Altered mental status, delirium, obtundation, coma, convulsions and seizures, muscle cramps or tetany, neuromuscular hyperexcitability, paresthesias.

4.9Overdose

Overdose can lead to hypervitaminosis, hypercalciuria, and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and, in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment should consist of stopping all intakes of vitamin D and providing rehydration. Serum and urine calcium levels should be monitored in patients with suspected vitamin D toxicity. Standard therapy includes restriction of dietary calcium, hydration, and systemic glucocorticoids in patients with severe hypercalcemia. Dialysis to remove vitamin D would not be beneficial.

Treatment of Hypercalcaemia: Treatment with calcium must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Emptying of the stomach should be done in patients with impaired consciousness. Rehydration and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids must be initiated. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, electrocardiogram (ECG) and central venous pressure should be monitored.

5. Pharmacological Properties

5.1 Mechanism of Action

Vitamin D, a fat soluble vitamin, is produced endogenously in the skin and is important for calcium homeostasis and for optimal skeletal health. Cholecalciferol, also called vitamin D_3, is produced naturally in the skin when skin exposed to ultraviolet rays of sunlight.

When ultraviolet rays from sunlight strike the skin, 7-dehydrocholesterol (a precursor of vitamin D) will be converted to cholecalciferol (vitamin D_3). Cholecalciferol requires metabolic activation. The circulating vitamin D_3 undergoes hydroxylation in the liver with the help of the enzyme, 25-

hydroxylase to form 25-hydroxycholecalciferol (calcidiol), which is the predominant circulating metabolite. Further hydroxylation in the kidneys forms 1, 25-dihydroxycholecalciferol (calcitriol) with the help of enzyme 1-alpha-hydroxylase. Calcidiol possesses some intrinsic activity, but calcitriol is the most active metabolite of vitamin D.

5.2Pharmacodynamic Properties

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or deformed. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Extra-skeletal health benefits of vitamin D include chronic disease prevention (heart disease, diabetes), regulation of immune function (autoimmune disease prevention – multiple sclerosis, type 1 diabetes, rheumatoid arthritis), regulation of cell growth (cancer prevention - colon, breast), etc.

5.3Pharmacokinetic Properties

Absorption: Vitamin D is well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption.

Distribution: Vitamin D and its metabolites circulate in the blood, bound to a specific alpha-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Cholecalciferol has a slow onset and a long duration of action.

Metabolism: Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxy-cholecalciferol (calcidiol). It is then further converted in the kidneys to 1,25- dihydroxy-cholecalciferol (calcitriol). Calcitriol is the most potent steroid hormone derived from cholecalciferol. Calcitriol/1,25-dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D that is not metabolized is stored in adipose and muscle tissues.

Excretion: Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces, with only small amounts appearing in urine. There is some entero-hepatic recycling, but it is considered to have negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

6. Nonclinical Properties

6.1 Animal Toxicology

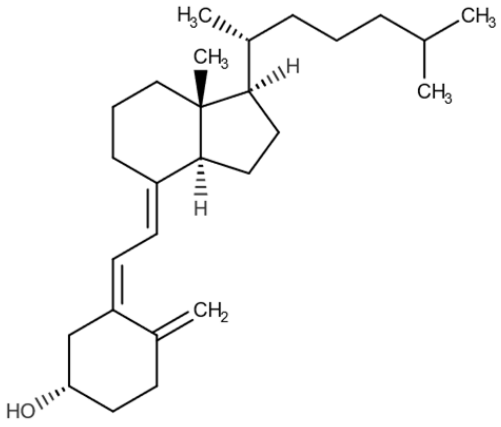
Pre-clinical studies conducted in various animal species have demonstrated that toxic effects occur in animals at doses much higher than those required for therapeutic use in humans.
In toxicity studies at repeated doses, the effects most commonly reported were increased calciuria and decreased phosphaturia and proteinuria. Hypercalcaemia has been reported in high doses. In a state of prolonged hypercalcaemia, histological alterations (calcification) were more frequently borne by the kidneys, heart, aorta, testes, thymus and intestinal mucosa.
At doses equivalent to those used therapeutically, cholecalciferol has no teratogenic activity. However, cholecalciferol has been shown to be teratogenic at high doses in animals. Cholecalciferol has no potential mutagenic or carcinogenic activity.

7. Description

BLUVIT-D_3 Sachet contain white granular powder.

BLUVIT-D_3 Sachet contains 60,000 IU of cholecalciferol for oral administration in adults and children.

Cholecalciferol is a steroid hormone produced in the skin when exposed to ultraviolet light or obtained from dietary sources.
Vitamin D_3 (cholecalciferol) appears as fine colorless (or cream colored) crystalline powder which is insoluble in water.
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:



Inactive ingredients (excipients) of BLUVIT-D_3 Sachet contain Colloidal Silicon Dioxide, Flavour Vanila, Flavour BTM Mint DM, Flavour Orange, Methyl Paraben, Propyl Paraben, Sucralose, Lactose, and Starch.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

Sachet of 1 gram.

8.4Storage and Handling Instructions

Store protected from light and moisture at temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Pour the contents of the sachet into a glass of non-carbonated water. Shake/stir the contents until the granules get dispersed and then drink it immediately.
- Instruct patients to take BLUVIT-D_3 Sachets once a week initially for 6 to 8 weeks and thereafter once a month (as advised by your doctor). BLUVIT-D_3 Sachet to be taken preferably with the main meal of the day (for better absorption and effect).
- Patients should be advised to avoid this formulation (because of higher dosage strength) during pregnancy and lactation.
- Advice patients to consult their doctor before taking this therapy if they have kidney or liver function related problems.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No.: 51/UA/SC/P-2013.
Date of FDA Product Permission: 19/07/2016.

12. Date of Revision

March 2021.

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.