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 (Vitamin D_3) Drops
(Brand Name: BLUVIT®-D_3 Drops)

2. Qualitative and Quantitative Composition

Each ml contains:
Cholecalciferol IP ..... 800 IU.
(In a nano droplet form)
Flavoured base ……..... q.s.
(1 ml equal to approximate 30 drops)
Colour: Ponceau 4R.
Appropriate overages of vitamin added to compensate loss on storage.

3. Dosage Form and Strength

Dosage Form: Oral Drops.
Dosage Strength: Cholecalciferol (Vitamin D_3) 800 IU per ml.

4. Clinical Particulars

4.1 Therapeutic Indication

BLUVIT-D_3 Drops is indicated for treatment of vitamin D deficiency or insufficiency.
BLUVIT-D_3 Drops are also indicated in prevention of vitamin D deficiency when there is increased risk of deficiency or an increased demand for vitamin D.

4.2Posology and Method of Administration

For oral administration.

Children

1. **Treatment of vitamin D deficiency or insufficiency:**
   - For infants and toddlers aged 0 to 1 year: 2000 IU/day of vitamin D_3 to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 400 to 1000 IU/day.
   - For children aged 1 to 18 years: 2000 IU/day of vitamin D_3 for at least 6 weeks to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600 to 1000 IU/day.

2. Prevention of vitamin D deficiency when there is increased risk of deficiency:

- For infants and toddlers aged 0 to 1 year: 400 to 1000 IU/day of vitamin D_3.
- For children aged 1 to 18 years: 600 to 1000 IU/day of vitamin D_3.

The current American Academy of Pediatrics (AAP) recommendation is a minimum dietary intake of 400 IU/day for neonates, children and adolescents. If this amount cannot be achieved through their normal diet, a vitamin D supplement should be administered. Exclusively breast fed infants should receive 400 IU/day of an oral liquid vitamin D product. Supplementation should begin within days of birth, given that vitamin D deficiency can start early in life.

Obese children and children on anticonvulsants, glucocorticoids, and antifungal (such as ketoconazole) medications may require at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement.

Adults

Recommended dietary allowance (RDA) of vitamin D_3 is 600 IU/day. People who are at risk of vitamin D deficiency may require 1500 to 2000 IU/day. For the treatment of vitamin D deficiency in adults, 6000 IU/day of vitamin D_3 may be required to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500 to 2000 IU/day.

To treat vitamin D deficiency in obese patients (BMI 30 kg/m^2), patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism (such as anticonvulsants, glucocorticoids, ketoconazole), a two to three times higher dose of vitamin D_3 i.e., at least 6000 to 10,000 IU/day, is recommended to maintain a serum 25(OH)D level above 30 ng/ml, followed by maintenance therapy of at least 3000 to 6000 IU/day.

Elderly (above 70 years): Recommended dietary allowance (RDA) of vitamin D_3 is slightly higher i.e., 800 IU/day in people above 70 years of age. Treatment of vitamin D deficiency or those who are at risk of vitamin D deficiency may require dosage regimen same as like adults.

Table: Serum 25(OH)D Levels and Vitamin D Status

Serum 25(OH)D ng/ml	**Vitamin D Status**
<20	Deficiency
20-30	Insufficiency
30-100	Sufficiency
>200	Toxicity

Vitamin D is well absorbed from the gastro-intestinal tract in the presence of bile. Therefore, BLUVIT-D_3 Drops to be administered preferably with food.
Or, as prescribed by the physician.

4.3Contraindications

BLUVIT-D_3 Drops are contraindicated in the following:

- Hypersensitivity to cholecalciferol (vitamin D_3) 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 carefully administered when prescribing other products 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 is a precursor of calcitriol. Thus, while using cholecalciferol, any medications containing calcitriol should be used with caution.
Other vitamin D compounds and their derivatives, including food-stuff which may be fortified with vitamin D should be withheld during treatment with BLUVIT-D_3 drops.
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 is 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 they 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, caution 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 dose of ketoconazole. Higher doses of cholecalciferol may be necessary if these drugs are administered simultaneously.

Corticosteroids: A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit calcium absorption. Higher doses of cholecalciferol is required if these drugs are administered concurrently.

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.

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

Recommended dietary allowance (RDA) for pregnant women is 600 IU/day of vitamin D_3. Pregnant women are at high risk for vitamin D deficiency, which increases the risk of preeclampsia and cesarean section. Thus, a higher dosage of vitamin D is generally required in pregnant women. Pregnant women who are at risk of vitamin D deficiency may require 1500 to 2000 IU/day of vitamin D_3.

Lactating Women

The recommended daily regimen of vitamin D_3 for breast feeding women is 600 IU. However, in vitamin D deficiency states, lactating women may require 1500 to 2000 IU/day of vitamin D_3. Vitamin D_3 and some of its active metabolites pass into breast milk. To satisfy their infant's

requirement, nursing mothers may require 4000 to 6000 IU/day of vitamin D_3, if they choose not to give a vitamin D supplement to their infant.

Paediatric Patients

BLUVIT-D_3 Drops can be safely administered to infants and children. For dosage, please refer 'Posology and Method of Administration' section.

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. In people above 70 years old, recommended dietary allowance (RDA) of vitamin D_3 is 800 IU/day. People who are at risk of vitamin D deficiency may require 1500 to 2000 IU/day.

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 cholecalciferol is not metabolized normally thus, 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 on the ability to drive or use machines. However, this effect is unlikely to occur.

4.8Undesirable Effects

Side effects reported with the use of vitamin D may include 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 has been reported rarely. 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 of vitamin D 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 it gets exposed to the 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 and 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 with the help of enzyme 1-alpha-hydroxylase forms 1, 25-dihydroxycholecalciferol (calcitriol). 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 an adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemia 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

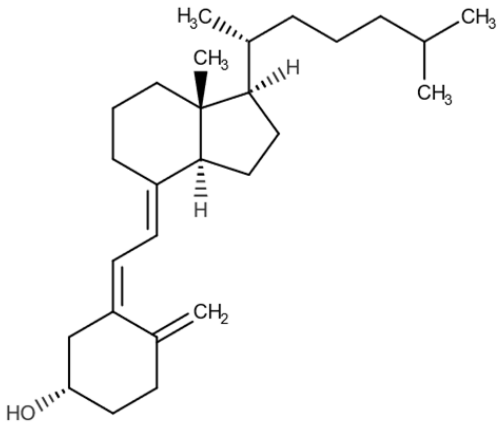
state of prolonged hypercalcaemia, histological alterations (calcification) were more frequently borne by the kidneys, heart, aorta, testes, thymus and intestinal mucosa.
At doses equivalent to those used therapeutically, cholecalciferol has no teratogenic activity. However, cholecalciferol has been shown to be teratogenic at high doses in animals. Cholecalciferol has no potential mutagenic or carcinogenic activity.

7. Description

BLUVIT-D_3 Drops are pink colored, clear, flavored oral drops.

BLUVIT-D_3 Drops contains 800 IU of cholecalciferol per ml for oral administration in infants 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 Drops contain Cremophore RH 40, Vitamin E Acetate, Sodium Benzoate, Potassium Sorbate, Sucralose, Xylitol, Glycerin, Mallic Acid, Liquid Strawberry Flavour, Ponceau 4R, and Purified Water.

8. Pharmaceutical Particulars

8.1 Incompatibilities
None known.

8.2Shelf-life
18 months.

8.3Packaging Information
30 ml bottle with 1 ml dropper.

8.4Storage and Handling Instructions
Store in a cool dry place at a temperature below 25 °C, protect from direct sunlight.
Keep out of reach of children

9. Patient Counseling Information
Administration Instructions to Patients and Parents (care givers)

- Instruct patients/parents to use this medicine exactly as prescribed by their doctor. Do not change the dose or stop therapy without consulting doctor.
- Neonates, infants, children, pregnant women or lactating mothers can use this product safely.
- Advice patients/parents that it is preferable to use BLUVIT-D_3 Drops with foods (for better absorption and effect).
- Shake bottle well before each use.
- Advice patients/parents to consult their doctor before taking this therapy if they have any kidney or liver function related problems; caution should be exercised.

10. Details of Manufacturer
Tirupati Medicare Limited,
Nahan Road, Paonta Sahib,
Distt. Sirmour (H.P.) 173 025.

11. Details of Permission or License Number with Date
Mfg. Lic. No.: MB/07/553.
Date of FDA Product Permission: 15/06/2017.

12. Date of Revision
March 2021.

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BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
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