ERGOCALCIFEROL, CHOLECALCIFEROL
(Vitamin D)

### THERAPEUTICS

#### Brands
- Deltalin
- Drisdol
- Calcitidol
- Multiple, also sold over-the-counter without a prescription as nutritional agent

#### Generic
- Vitamin D₂ (ergocalciferol)
- Vitamin D₃ (cholecalciferol)

#### Class
- Vitamins

#### Used for
(FDA approved in bold)
- Nonspecific chronic back pain in patients with vitamin D insufficiency or deficiency
- Proximal weakness and fatigue in patients with vitamin D insufficiency or deficiency
- Rickets
- Osteomalacia
- Hypoparathyroidism
- Chronic kidney disease

#### How the Drug Works
- Vitamin D is a group of liposoluble steroids. The body can synthesize vitamin D₃ in the skin when sun exposure is adequate. Otherwise, it must be obtained from diet as vitamin D₂ (ergocalciferol) from fungi and plants or as vitamin D₃ (cholecalciferol) from animal sources. Skin characteristics modify the amount of vitamin D formed with African-American people having the greatest difficulties of vitamin D synthesis since pigmentation decreases vitamin D production under sun exposure. Above a latitude of 42 degrees north, from November to February, sunlight is ineffective for the synthesis of vitamin D in the skin. A study conducted in Boston, MA, demonstrated that 52% of Hispanic and African-American adolescents were vitamin D deficient
- Vitamin D deficiency has been shown to contribute to clinical symptoms of neuromuscular dysfunction and nonspecific musculoskeletal pain. Vitamin D acts as a steroid hormone; it enters cells and binds to a specific nuclear receptor or vitamin D receptor (VDR) that triggers a variety of gene expression in more than 30 different tissues. It has an important role in the regulation of calcium transport and protein synthesis in the muscle cell, and increases the calcium pool which is essential for muscle contraction. Of note, vitamin D deficiency promotes parathyroid hormone (PTH) secretion and elevation of its plasma levels. Hyperparathyroidism appears to induce proteolysis of muscle proteins and impairment in oxidation of long-chain fatty acids in skeletal muscle, possibly contributing to the pathogenesis of osteomalacic myopathy
- The serum concentration of 25-hydroxyvitamin D is typically used to determine vitamin D status. Long-standing vitamin D insufficiency, generally categorized as 25-OH vitamin D level between 10 and 20 ng/mL, has been associated with impaired neuromuscular function, including increased body sway. More severe vitamin D insufficiency or deficiency, with a 25-OH vitamin D level of less than 10ng/mL, has been associated with weakness and widespread pain. The weakness is typically of proximal type, while the musculoskeletal pains are more generalized and can affect the spine and hips. Of note, patients with vitamin D deficiency may present with widespread pain, leading to alternative diagnoses such as fibromyalgia and rheumatological disorders

#### How Long until It Works
- Undetermined, but at least a 12-week trial is recommended

#### If It Works
- Treatment cycles can be repeated

#### If It Doesn’t Work
- Alternative supplements or analgesic medications as per physician’s recommendations

#### Best Augmenting Combos for Partial Response or Treatment-Resistance
- None

#### Tests
- None

### ADVERSE EFFECTS (AEs)

#### How the Nutraceutical Causes AEs
- Vitamin D toxicity usually results from taking supplements in high excess for months. In healthy adults, sustained intake of more than...
50,000 IU/day can produce hypercalcemia related toxicity after several months. Of note, 40,000 IU/day in infants has produced toxicity within 1 month.

- Levels of 25-hydroxy-vitamin D that are consistently above 150–200 ng/mL are thought to be potentially toxic. Hypercalcemia is typically the cause of symptoms. It is recommended to periodically measure serum calcium in individuals receiving large doses of vitamin D. Vitamin D overdose causes hypercalcemia, and the main symptoms of vitamin D overdose are those of hypercalcemia: lethargy, anorexia, nausea, and vomiting, frequently followed by polyuria, polydipsia, weakness, and, ultimately, renal failure. Vitamin D toxicity is treated by discontinuing vitamin D supplementation and restricting calcium intake.

**Life-Threatening or Dangerous AEs**

- Hypervitaminosis D can cause hypercalcemia with anorexia, nausea, weakness, weight loss, constipation, mental changes with lethargy. There is impairment of renal function with polyuria, nocturia, polydipsia, and hypertension.
- Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs.
- Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism).
- The treatment of hypervitaminosis D with hypercalcemia consists in immediate withdrawal of the vitamin, a low calcium diet, generous intake of fluids, along with symptomatic and supportive treatment.

**Weight Gain**

- Undetermined

**What to Do about AEs**

- If any of relevance, stop the supplement

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### How to Dose

- 1–70 years of age: 600 IU/day and for older than 71 years of age: 800 IU/day
- Obese individuals require 2–3 times more than for their respective age groups
- In case of vitamin D insufficiency or deficiency weekly doses of 50,000 IU units can be given under physician’s supervision
- For a more aggressive treatment in patients with severe deficiency, the 50,000 IU can be given daily for the first 3–5 days followed by weekly doses to be taken under close physician’s supervision
- If necessary for maintenance under physician’s supervision, daily doses may be titrated up to 4000 IU

### Overdose

- It can cause irreversible renal insufficiency. Hypercalcemic crisis with dehydration, stupor, coma, requires vigorous treatment. The first step should be hydration of the patient. Intravenous saline may quickly and significantly increase urinary calcium excretion. A loop diuretic (furosemide or ethacrynic acid) may be given with the saline infusion to further increase renal calcium excretion. Other reported therapeutic measures include dialysis or the administration of citrates, sulfates, phosphates, and corticosteroids. With appropriate therapy, recovery is the usual outcome when no permanent damage has occurred. Deaths via renal or cardiovascular failure have been reported. The LD50 in animals is unknown. The toxic oral dose of ergocalciferol in the dog is 4 mg/kg.

### Long-Term Use

- Supplementation is recommended, but contraindicated in patients with hypercalcemia, abnormal sensitivity to the toxic effects of vitamin D, and hypervitaminosis D

### Habit Forming

- No

### How to Stop

- No guidelines necessary

### Pharmacokinetics

- There is a time lag of 10–24 hours between the administration of vitamin D and the initiation of its action in the body due to the necessity of synthesis of the active metabolites in the liver and kidneys. The in vivo synthesis of the major biologically active metabolites of vitamin D occurs in two steps. The first hydroxylation takes place in the liver (to 25-hydroxyvitamin D or calcidiol) and the second in the kidneys.
Calcitriol is a potent ligand of the vitamin D receptor, which mediates most of the physiological actions of the vitamin. The conversion of calcidiol to calcitriol is catalyzed by the enzyme 25-hydroxyvitamin D3 1-alpha-hydroxylase, the activity of which is increased by parathyroid hormone (PTH) (and additionally by low calcium or phosphate). PTH is responsible for the regulation of calcitriol in the kidneys. When synthesized, calcitriol circulates as a hormone, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. Vitamin D prevents rickets in children and osteomalacia in adults, and, together with calcium, helps to protect older adults from osteoporosis. Vitamin D also affects neuromuscular function, inflammation, and influences the action of many genes that regulate the proliferation, differentiation, and apoptosis of cells. Vitamin D metabolites promote the active absorption of calcium and phosphorus by the small intestine, thus elevating serum calcium and phosphate levels sufficiently to permit bone mineralization. Vitamin D metabolites also increase the reabsorption of calcium and perhaps also of phosphate by the renal tubules.

Drug Interactions
- Administration of thiazide diuretics to hypoparathyroid patients who are concurrently being treated with ergocalciferol may cause hypercalcemia.

SPECIAL POPULATIONS

Renal Impairment
- Adequate supplementation recommended

Hepatic Impairment
- Adequate supplementation recommended

Cardiac Impairment
- Undetermined

Elderly
- Certain populations are more prone to developing vitamin D deficiency, such as the elderly, institutionalized, and disabled. Elderly people have a decreased capacity to synthesize vitamin D in their skin and require higher daily doses of supplementation than younger people. A few published reports have also suggested that the absorption of orally administered vitamin D may be attenuated in elderly compared to younger individuals.

Infants
- 0–12 months: 400 IU/day under medical supervision

Children and adolescents
- Well tolerated at the recommended dietary allowance
- Studies have shown a large number of younger individuals to be affected by vitamin D deficiency
- When given at higher doses for medical indications, dosage must be individualized and taken under medical supervision

Pregnancy
- Pregnant women should consult a doctor before taking a vitamin D supplement
- Animal reproduction studies have shown fetal abnormalities in several species associated with hypervitaminosis D. These are similar to the supravalvular aortic stenosis syndrome described in infants characterized by supravalvular aortic stenosis, elfin facies, and mental retardation. For the protection of the fetus, therefore, the use of vitamin D in excess of the recommended dietary allowance is a category C and during normal pregnancy should be avoided unless, in the judgment of the physician, potential benefits outweigh the significant hazards involved.

Breast-Feeding
- Breast-feeding women should consult a doctor before taking a vitamin D supplement.

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Adequate supplementation may improve response to standard treatment in patients with chronic musculoskeletal pain, and may help with comorbidities such as fatigue and weakness.

Potential Disadvantages
- Unknown

Pearls
- 1 USP unit of vitamin D₂ is equivalent to 1 International Unit (IU), and 1 μg of vitamin D₂ is equal to 40 USP units.
One proposed mechanism for pain in patients with vitamin D deficiency induced osteomalacia is that insufficient calcium phosphate levels result in impaired mineralization of the collagen matrix of bone. Undermineralized matrix is hydrated and expands, supposedly causing pressure within the bone and underneath the periosteal covering. It is conceivable that increased mechanical pressure can reach a sufficient force to activate mechano-sensitive nociceptors in the cortical and trabecular bone and in the periosteum. The activation of bone nociceptors can become clinically relevant to elicit bone pain and deep hyperalgesia. It is known, for example, that gentle pressure on superficial bones, such as tibia or sternum, can cause pain in patients with vitamin D deficiency induced osteomalacia.

Multiple authors have described resolution of diffuse body aches and pain with normalization of 25-OH vitamin D serum levels. Patients with widespread pain and proximal muscle weakness secondary to osteomalacic myopathy experienced dramatic improvement in their symptoms after receiving vitamin D supplementation. Patients with vitamin D deficiency who had diffuse back and leg pain unresponsive to standard analgesic medications reported dramatic improvement in their pain following administration of 50 000 IU of vitamin D. Patients with vitamin D deficiency, and back, leg, and rib pain responded to vitamin D high-dose supplementation within 3 months.

Exposure to sunlight for extended periods of time does not cause vitamin D toxicity. Within about 20 minutes of ultraviolet exposure in light skinned individuals, the concentrations of vitamin D precursors produced in the skin reach equilibrium. According to some sources, endogenous production with full body exposure to sunlight is approximately 10 000 IU/day.

Suggested Reading


Glerup H, Mikkelsen K, Poulsen L, *et al*. VitD deficiency myopathy without biochemical signs of...


