Oravil®

VITAMIN D3 (CHOLECALCIFEROL)
AQUEOUS SOLUTION (ORAL)

MADE IN ARGENTINA - Prescription medicine

COMPOSITION

Each bottle with 2 mL contains the following: Cholecalciferol (vitamin D_3) 2.5 mg (100,000 IU). Excipients: butylhydroxytoluene, saccharin, orange flavoring, corn oil.

Therapeutic action:

Oral Vitamin D therapy. Cholecalciferol promotes calcium and phosphate absorption for normal bone calcification. Cholecalciferol plays a role, together with parathyroid hormone and calcitonin, in controlling calcemia by the increase of serum calcium and phosphate.

ATC Code: A11CC05

INDICATIONS

- Prevention and treatment against vitamin D deficit caused by lack of intake, poor sun exposure or by fat intestinal malabsorption.
- Rickets and Osteomalacia.
- Prevention and treatment against osteoporosis in patients with poor vitamin D/calcium food intake.

PHARMACOLOGICAL CHARACTERSTICS

Pharmacological action:

Vitamin D promotes calcium and phosphate absorption for normal bone calcification. Exposure to sunlight UV rays leads to cholecalciferol formation (vitamin D). Calcifediol is converted to calcitriol through 25-hydroxylation, primarily in the kidney. When calcitriol binds to the receptor in intestinal mucosa, the ligand-receptor complex is translocated to the cell nucleus, probably creating a calcium binding protein, increasing intestinal absorption. Calcitriol, together with the parathyroid hormone (PTH), regulates calcium ions transport from the bone to extracellular fluid, leading to calcium homeostasis. It binds to transport globulins and is deposited mainly in kidney and fat tissue. Calcitriol does not require metabolic activation, and degradation is produced partially in the kidney. Its half-life in plasma is 3 to 8 hours, and its action to increase serum calcium starts after 2 to 6 hours (orally). Calcitriol remains in plasma from 1 to 2 days after oral administration.

Pharmacokinetics:

Cholecalciferol is absorbed efficiently in the small intestine. Bile is essential for vitamin D adequate absorption and large amount of bile is in lymph chylomicrons. People with intestinal bypass surgery, shortened bowel or with any inflammatory disease may suffer from vitamin D malabsorption. Hepatic and biliary dysfunctions may also decrease vitamin D absorption substantially.

Once absorbed, it circulates through plasma bound to vitamin D-binding protein (a specific alpha-globulin). It disappears from plasma with a half-life of 19-25 hours, but it is distributed and stored in fatty tissue for long periods. It is mainly excreted through bile, and low excretion percentage through urine.

DOSAGE AND ROUTE OF ADMINISTRATION

Vitamin D dosage must be adjusted to each case at the discretion of the prescribing doctor. Oravil® is for oral use. It must be administered preferably with foods. The bottle content may be administered as is or diluted with a little water or milk.

- **Rickets prevention in children under 5 years:** one full bottle every three months up to the fifth year. This dose may duplicate if the child has low exposure to sunlight or in case of hyperpigmentation. Dose must not exceed 10 to 15 milligrams/year (that is, 4 to 6 bottles/year).
- **Prevention in older children and adolescents having vitamin D deficiency:** one full bottle every three months in low sunlight periods.
- **Vitamin D deficiency prevention in pregnant women: one monodose vial:** administered only once towards the 6th month of pregnancy.
- **Prevention in adults and elderly having vitamin D deficiency:** one bottle every three months.
- **Treatment in adults and elderly having vitamin D deficiency:** one to two full bottles per month.

CONTRAINDICATIONS
Vitamin D hypersensitivity.
Hypercalcemia, hypervitaminosis D, renal osteodystrophy with hyperphosphatemia. Additionally, the risk/benefit ratio must be highly considered in patients with the following: Arteriosclerosis, heart failure, hyperphosphatemia, renal failure and sarcoidosis.

PRECAUTIONS AND WARNINGS
The therapeutic range between therapeutic and toxic doses is narrow. Doses must be adjusted as soon as clinical improvement is observed. Administration must be conducted under medical supervision. Intake of vitamin D-fortified foods must be readjusted to avoid vitamin D overdose or similar.
Pregnancy: no problems with daily vitamin D intake have been reported. However, excess of vitamin D may be harmful to the mother and the fetus. Pregnant women with hypersensitivity to vitamin D effects may experience hypercalcemia and hypoparathyroidism, and lactating infants may have Williams´syndrome, mental retardation and congenital aortic stenosis.
Lactation: although low amounts of vitamin D metabolites are present in breast milk, no problems with normal daily intake in humans have been reported. Some lactating infants may be susceptible even to low doses of vitamin D.
Pediatric use: growth may be interrupted in children with prolonged daily administration of vitamin D 1.800 IU. Pediatric use must be conducted under strict medical surveillance.
Use in the elderly: in older adults and the elderly, vitamin D responses are similar to those observed in young adults.
Patients under anticonvulsant therapy: these patients may require vitamin D supplements to prevent osteomalacia.

INTERACTIONS
Bisphosphonates (such as alendronate, ibandronate and others), gallium nitrate and plicamide used for the treatment against hypercalcemia may antagonize vitamin D effects. Antacids based on aluminum salts reduce absorption of fat soluble vitamins such as vitamin D. Barbiturates and anticonvulsant drugs may reduce the vitamin D effect by acceleration of hepatic enzyme induction. In hypercalcemia therapy, vitamin D may antagonize the calcitonin effects if administered concomitantly. Thiazide diuretics and calcium preparations together with vitamin D may increase the risk of hypercalcemia. Cholestyramin, cholestipol and/or mineral oils reduce intestinal absorption of vitamin D; therefore, if they must be coadministered, vitamin D dose must be increased properly. In patients receiving digitalis, vitamin D coadministration may produce cardiac arrhythmias, and coadministration with phosphate-based salts may induce hyperphosphatemia.

ADVERSE REACTIONS
Excess of vitamin D (by a single dose or by prolonged therapy) may cause severe overdosage. Hypercalcemia induced by chronic vitamin D administration may cause massive vascular calcification, nephrocalcinosis and other soft tissue calcification, leading to hypertension and renal injury. These events may occur mainly when hypercalcemia appears with hyperphosphatemia. In case of vitamin D overdose, death may occur due to renal or vascular injury. Doses that may cause poisoning depend on each individual susceptibility.
The main adverse reactions observed include constipation (most frequent in children), diarrhea, mouth dryness, headache, increased thirst, anorexia, nausea, vomiting, tiredness. Severe cases include bone pain, arterial hypertension, nebulous urine, pruritus, muscle pain, weight loss and/or seizures.

OVERDOSE
Treatment against hypervitaminosis consists of immediate interruption of vitamin D, a low-calcium diet, increased fluid intake, urinary acidification during detoxification and supportive therapy. Additional therapeutic actions include administration of citrates, sulphates, phosphates, corticosteroids, ethylenediaminetetraacetic acid (EDTA) and mithramycin In case of accidental overdose, proceed to IV hydration with saline solution if hypercalcemic crisis occurs in order to promote calcium elimination, adding loop diuretics if necessary.

DOSAGE FORMS
Pack containing one bottle with 2 mL.

STORAGE CONDITIONS
Keep the product in its original package. Keep at room temperature (15°C to 25°C) and protected from light.
Keep this and all medicines out of the reach of children. Keep this medication in its original package.

Medicinal product authorized by the Ministry of Health. Certificate Nº 58.209.
Manufactured by Laboratorio Elea Phoenix S.A., Av. Gral. Lemos Nº 2809, Los Polvorines, Buenos Aires, Argentina.

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