SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEVIT-3 50,000 IU Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains:

Active Substance:
Cholecalciferol…….....50,000 IU
(Equivalent to 1.25 mg Cholecalciferol)

Excipient(s) with known effect:
Sorbitol……. 6.72 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsules.
Biconvex, oval, mustard yellow colored soft capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEVIT-3 is indicated in the therapy, maintenance therapy, and prophylaxis of Vitamin D deficiency.

4.2 Posology and method of administration

Posology/frequency and duration of administration

Each soft capsule contains 50,000 IU of vitamin D_3.
The doctor will decide how to use the medicine. It should be used according to the doctor's advice.

Age Group	Recommended Dose for Prophylaxis / Maintenance	Vitamin D Deficiency Treatment Dosage		Maximum Tolerated Dose for Maintenance Treatment and Prophylaxis in Risk Groups
		Daily Treatment**	Weekly Administration	
Newborn	400 IU/day (10 mcg/day)	1,000 IU/day (25 mcg/day)	No	1,000 IU/day (25 mcg/day)
1 month to 1 year	400 IU/day (10 mcg/day)	2,000-3,000 IU/day (50-75 mcg/day)	No	1,500 IU/day (37.5 mcg/day)
1 year to 10 years	400-800* IU/day (10-20 mcg/day)	3,000-5,000 IU/day (75-125 mcg/day)	No	2,000 IU/day (50 mcg/day)
11 years to 18 years	400-800* IU/day (10-20 mcg/day)	3,000-5,000 IU/day (75-125 mcg/day)	No	4,000 IU/day (100 mcg/day)
Adults over 18 years	600-1,500 IU/day (15-37.5 mcg/day)	7,000-10,000 IU/day (175-250 mcg/day)	50,000 IU/week (1,250 mcg/week)***	4,000 IU/day (100 mcg/day)

** Can be increased up to 1,000 IU when necessary.*
*** Can be taken up to 6-8 weeks.*
**** If weekly dosage is preferred to daily dosage, a single dose of 50,000 IU can be used for up to 6-8 weeks. More than 50,000 IU of Vitamin D at once is not recommended.*

The routine use of medicines containing vitamin D during pregnancy is not recommended. However, they should be used under the supervision of a physician when necessary.

The maximum dose should not exceed 1,000 IU/day in the use of medicines containing Vitamin D for the purpose of prophylaxis during pregnancy.

Method of administration
DEVIT-3 is administered orally.
The capsules should be swallowed as whole with some water.
Patients are advised to take DEVIT-3 preferably with a meal (see section 5.2).

Additional information on special populations
Renal impairment:
DEVIT-3 should not be used in patients with severe renal impairment. It should be used with caution in patients with moderate and mild renal impairment.

Hepatic impairment
No dose adjustment is required.

Pediatric population
It should not be used in children and adolescents (patients under 18 years of age).

Geriatric population
Used as adults.

4.3 Contraindications

DEVIT-3 is contraindicated
- In patients with hypersensitivity to the vitamin D or any of the excipients listed in section 6.1,
- In patients with hypercalcemia and/or hypercalciuria, or in conditions that may result in hypercalcemia and/or hypercalciuria,
- In case of nephrolithiasis (kidney stone) and nephrocalcinosis (ectopic deposit of calcium salts in the renal parenchyma, renal calcification),
- In severe renal impairment,
- In case of hypervitaminosis D,
- In children and adolescents (patients under 18 years of age).

4.4 Special warnings and precautions for use

DEVIT-3 should be used cautiously in patients with mild to moderate renal impairment and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. Since cholecalciferol, the form of Vitamin D, cannot normally be metabolized in patients with severe renal impairment, other forms of Vitamin D should be used in those patients.

Caution is required in patients receiving treatment for cardiovascular disease (see section 4.5).

DEVIT-3 should be used with particular caution in patients treated with benzothiadiazine derivatives (see section 4.5 Interaction with other medicinal products and other forms of interaction) and in immobilized patients (risk of hypercalcemia and hypercalciuria). Calcium levels in plasma and urine should be monitored in these patients.

DEVIT-3 should be prescribed with caution in patients with sarcoidosis, as increased metabolism of conversion to the active form of vitamin D may pose a risk. Serum and urinary calcium levels should be monitored during treatment with DEVIT-3 in these patients.

It should not be used in patients with pseudohypoparathyroidism (the need for vitamin D; normal susceptibility to vitamin D may sometimes reduce with the risk of prolonged overdose). In such cases, more manageable vitamin D derivatives are available.

The total dose of vitamin D_3 should be adjusted by evaluating the patient's intake of food enriched with vitamin D_3, drinking milk enriched with vitamin D_3, and the patient's exposure to the sun.

There is no conclusive evidence of causality between vitamin D_3 supplementation and renal stone formation, but the use of calcium supplements, especially with vitamin D_3, is thought to increase the risk of stone formation. The need for additional calcium supplementation should be considered individually for patients. Calcium use should be under close medical supervision in patients who require calcium supplementation with DEVIT-3 therapy.

Oral intake of high-dose vitamin D_3 (500,000 IU once a year bolus) has been reported to cause an increased risk of fracture in elderly patients, with the greatest increase seen within the first 3 months after dosing.

With a daily dose exceeding 1,000 IU of vitamin D_3, serum calcium values should be monitored during long-term treatment.

The routine use of medicines containing vitamin D during pregnancy is not recommended. However, they should be used under the supervision of a physician when necessary.

When using medicines containing Vitamin D for prophylaxis during pregnancy, the maximum dose should not exceed 1,000 IU/day.

DEVIT-3 contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of Vitamin D_3 by metabolic inactivation.

Thiazide diuretics reduce urinary excretion of calcium. Serum calcium should be monitored regularly during concomitant use of thiazide diuretics, as the risk of hypercalcemia increases.

Concomitant use with glucocorticoids may reduce the effect of vitamin D_3.

Administration of vitamin D_3 may increase the risk of digitalis toxicity (arrhythmia) in patients treated with drugs containing digitalis and other cardiac glycosides. Strict medical supervision is required,

with monitoring of serum calcium concentration and electrocardiography as needed.

Simultaneous treatment with ion exchange resins such as cholestyramine, colestipol, or orlistat, or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the renal enzyme, 25-hydroxyVitamin D-1-hydroxylase.

Rifampicin may reduce the effectiveness of cholecalciferol due to hepatic enzyme induction.

Isoniazid may reduce the effectiveness of cholecalciferol due to inhibition of the metabolic activation of cholecalciferol.

Additional information on special populations
No data available.

Pediatric population
No data available.

4.6 Pregnancy and lactation

Products containing high-dose vitamin D_3 are not recommended during pregnancy and lactation, and lower-dose vitamin D_3 should be used instead.

General recommendation
Pregnancy category is C.

Women of child-bearing potential/Contraception
Data on contraception are not available.

Pregnancy
There are no or limited data on the use of cholecalciferol in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Prolonged overdose should be avoided during pregnancy because the resulting prolonged hypercalcemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy in the child.

The routine use of medicines containing vitamin D during pregnancy is not recommended. However, they should be used under the supervision of a physician when necessary.

When using medicines containing Vitamin D for prophylaxis during pregnancy, the maximum dose should not exceed 1,000 IU/day.

During pregnancy, women should follow the advice of their doctors. Because their need for vitamin D_3 may vary depending on the severity of their disease and their response to treatment.

High-dose vitamin D is not recommended for the treatment in pregnant women.

Lactation
Vitamin D_3 and its metabolites pass into breast milk. Vitamin D_3 can be prescribed while

breastfeeding if necessary for the patient. This supplement does not replace vitamin D_3 in the newborn baby.
Overdose in infants by nursing mothers has not been observed, however, when prescribing supplemental vitamin D3 to a breastfed child, the practitioner should consider any additional vitamin D_3 dose given to the mother. Treatment with high-dose vitamin D is not recommended for women who are breastfeeding.

In addition, there is a risk of hypercalcemia in infants of nursing mothers who receive pharmacological doses of Vitamin D.

Reproduction ability / Fertility
No data on the effect of vitamin D_3 on fertility are available. However, normal endogenous levels of vitamin D are not expected to produce any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, DEVIT-3 is unlikely to affect the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are ranked according to system organ class and frequency using the following principles:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders
Uncommon: Hypercalcemia, hypercalciuria.

Skin and subcutaneous disorders
Rare: Pruritus, rash, urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
Ergocalciferol (vitamin D_2) and colecalciferol (vitamin D_3) have only a relatively narrow therapeutic index. In adults with normal function of the parathyroid glands, the threshold for vitamin D intoxication is 40,000 to 100,000 IU per day for 1 to 2 months. Infants and young children can react to much lower concentrations. Therefore, vitamin D should always be taken under medical supervision.

Overdose causes elevated serum and urea phosphorus levels, as well as hypercalcemic syndrome and calcium deposition in tissues and vessels, primarily nephrolithiasis, nephrocalcinosis in the kidneys.

DEVIT-3 should be discontinued if calcemia exceeds 10.6 mg/dl (2.65 mmol/l) or if the calciuria exceeds 300 mg/24 hours in adults or 4-6 mg/kg/day in children.

Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcemia. Symptoms of vitamin D intoxication are somewhat characteristic and manifest as nausea, vomiting, diarrhea initially, then constipation, loss of appetite, fatigue, headache, myalgia, joint pain, muscle weakness, persistent insomnia, azotemia, polydipsia and polyuria, and eventually dehydration. Typical biochemical findings include hypercalcemia, hypercalciuria, and increased serum 25-hydroxy-cholecalciferol concentrations.

Treatment
Symptoms of chronic vitamin D overdosage may require forced diuresis as well as administration of glucocorticoids or calcitonin.

Overdosage requires measures for treating the- often persisting and under certain circumstances life-threatening hypercalcemia.

The first measure is to discontinue the vitamin D preparation and begin rehydration; thus, it takes several weeks to normalize the hypercalcemia caused by vitamin D intoxication.

Depending on the degree of hypercalcemia, measures include a diet that is low in calcium or free of calcium, abundant liquid intake, increase of urinary excretion by means of the drug furosemide, as well as the administration of glucocorticoids and calcitonin.

If kidney function is adequate, calcium levels can be reliably lowered by infusions of isotonic sodium chloride solution (3–6 liters in 24 hours) with addition of furosemide and, in some circumstances, 15 mg/kg body weight/hour sodium edetate accompanied by continuous calcium and ECG monitoring. In oligoanuria, in contrast, hemodialysis (calcium-free dialysate) is necessary.

There is no specific antidote for vitamin D intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, cholecalciferol
ATC code: A11CC05

In its biologically active form, vitamin D_3 stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D_3. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active form of vitamin D_3.

5.2 Pharmacokinetic properties

The pharmacokinetics of vitamin D is well known.

General particulars
Exposure to sunlight: UVB light converts 7-dehydrocholesterol in the skin to cholecalciferol.

Absorption
Vitamin D_3 is well absorbed from the gastrointestinal tract in the presence of bile, there taking vitamin D_3 with the main meal of the day may facilitate its absorption.

Distribution
Vitamin D and its metabolites that pass into the blood bind to a specific α-globulin.

Biotransformation
Cholecalciferol is metabolized in the liver to 25-hydroxycholecalciferol ($25(OH)D^3$, calcidiol), which is the main storage form of vitamin D_3. Then $25(OH)D_3$ undergoes secondary hydroxylation in the kidney to form the predominant active metabolite, 1,25-hydroxycholecalciferol ($1,25(OH)_2D_3$, calcitriol).

Elimination
The metabolites circulate in the blood bound to a specific α–globin, vitamin D_3 and its metabolites are excreted mainly in the bile and feces. Small amounts of vitamin D can be found in the urine.

Characteristics in specific groups or patients
A 57% lower metabolic clearance rate is reported in subjects with renal impairment as compared with that of healthy volunteers.
Decreased absorption and increased elimination of vitamin D occurs in subjects with malabsorption.
Obese subjects maintain less vitamin D_3 levels because they have less sun exposure than healthy people. Therefore, they may need to use higher doses of vitamin D_3.

5.3 Preclinical safety data

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, 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.

Microcephaly, cardiac malformations, and skeletal abnormalities were observed in offsprings.. Offspring from pregnant rabbits treated with high doses of vitamin D had lesions anatomically similar to those of supravalvular aortic stenosis and offspring not showing such changes show vasculotoxicity similar to that of adults following acute vitamin D toxicity. Cholecalciferol were also fetotoxic in rats with fewer and smaller offsprings than pregnant rats receiving medium and high doses of vitamin D.

Colecalciferol has been shown to be teratogenic at high doses in animals.

At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.

Colecalciferol has no potential mutagenic or carcinogenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refined sunflower oil
Gelatin
Glycerin
Sorbitol
Deionized water
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C and in its original package in order to protect it from light and moisture.

6.5 Nature and contents of container

As the primary packaging material of DEVIT-3 50,000 IU Soft Capsules, a blister consisting of opaque PVC / Aclar and aluminum foil is used.
Supplied as 8 capsules with a package leaflet in a cardboard box.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA HOLDING A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)

2021/193

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 30.06.2021
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT