SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEVIT-3 1,000 IU Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains:
Active Substance:
Cholecalciferol……....1,000 IU
(Equivalent to 25 mcg Cholecalciferol)

Excipient(s) with known effect:
Sorbitol……. 6.72 mg
FD&C Yellow No:5……. 0.05 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsules.
Biconvex, oval, transparent, dark 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
One capsule contains 1,000 IU of cholecalciferol (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.

Additional information on special populations
Renal impairment:
DEVIT-3 should not be used in patients with severe renal impairment (see Section 4.3)

Hepatic impairment
No dose adjustment is required.

Pediatric population
Adolescents over 12 years old
DEVIT-3 should be given to children over 12 years of age only under medical supervision, depending on the patient's response to treatment and the severity of the disease.

Newborns and children (0-12 years)
It is not recommended for use in patients under 12 years of age.

Pregnant and lactating women:
DEVIT-3 1,000 soft capsule is not recommended during pregnancy unless the woman's clinical condition requires treatment.

Cholecalciferol and its metabolites pass into breast milk. Overdose has not been observed in infants induced by breastfeeding mothers, but the dose of vitamin D taken by the mother should be considered when prescribing products containing vitamin D to a breastfed child.

Geriatric population
Used as adults.

4.3 Contraindications

DEVIT-3 should not be used
- In patients with hypersensitivity to the active substance (cholecalciferol) or any excipient listed in section 6.1,
- In patients with hypercalcemia and/or hypercalciuria,
- In case of nephrolithiasis (kidney stone),
- In case of nephrocalcinosis (ectopic deposit of calcium salts in the kidney parenchyma) (kidney

calcification),
- In case of hypervitaminosis D,
- In patients with severe renal failure,
- In infants and children under 12 years of age.

4.4 Special warnings and precautions for use

DEVIT-3 soft capsules 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.

DEVIT-3 should not be used in patients predisposed to the formation of calcium-containing kidney stones.

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

During long-term treatment, the serum calcium values must be monitored and renal function should also be checked by measuring serum creatinine. Follow-up is essential especially in the elderly patients undergoing concomitant therapy with cardiac glycosides or diuretics and in patients with a high predisposition to form renal stones (see section 4.5).

DEVIT-3 should be prescribed with caution to patients suffering from sarcoidosis, because of the risk of increased metabolism of Vitamin D to its active form. These patients should be monitored with regard to the calcium levels in serum and urine.

When administering vitamin D supplements to patients, the intake of other medicines containing vitamin D or vitamin D from other sources should be considered.

The need for additional calcium supplements should be considered individually for each patient. Calcium supplements should be given under close medical supervision. In such cases, frequent monitoring of serum calcium levels and urinary calcium excretion is necessary.

Medical supervision is required during treatment to prevent hypercalcemia. In case of hypercalciuria (over 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function, the dose should be reduced or treatment discontinued.

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.

DEVIT-3 contains FD&C Yellow No:5, which is a azo dye. It may cause allergic reactions.

<u>Pediatric population</u>

It should be administered as stated in the posology/administration frequency and duration section. DEVIT-3 1,000 IU soft capsule should not be given to children and infants under 12 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

Phosphate infusions should not be administered to lower hypercalcemia of hypervitaminosis D because of the dangers of metastatic calcification.

Patients treated with cardiac glycosides may be more prone to elevated calcium levels, therefore ECG and calcium levels should be monitored. If the calcium levels in the urine exceeds 7.5 mmol/24 hours (300 mg/24 hours), dose reduction or discontinuation of therapy is recommended.

Since benzothiadiazine derivatives (thiazide diuretics) reduce urinary calcium excretion, concomitant administration with benzothiadiazine derivatives increases the risk of hypercalcemia. Therefore, plasma and urine calcium levels should be monitored in patients who will receive long-term treatment.

When cholecalciferol is used in combination with vitamin D analogues or metabolites, careful monitoring of serum calcium levels is recommended.

Anticonvulsant drugs such as phenytoin, phenobarbital, pyrimidone may reduce the effect of cholecalciferol as they cause hepatic enzyme induction.

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.

Drugs that cause fat malabsorption such as orlistat, liquid paraffin, and cholestyramine may impair the absorption of cholecalciferol.

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 kidney enzyme, 25-hydroxyvtamin D-1-hydroxylase.

Concomitant use with glucocorticoids may reduce the effect of vitamin D. Glucocorticoid steroids can increase the rate of metabolism and elimination of vitamin D. During concomitant use with glucocorticoid steroids, the dose of DEVIT-3 capsules may need to be increased.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category is C.

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

Pregnancy
DEVIT-3 should not be used during pregnancy unless the woman's clinical condition requires treatment with cholecalciferol at the dose necessary to correct the deficiency.

Pregnant women should follow their doctor's advice as their needs vary according to the severity of their disease and their response to treatment.

Animal studies and human experience have shown that when cholecalciferol is used during pregnancy, vitamin D excess causes physical and mental disorders and congenital heart and eye disorders due to hypercalcemia.

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.

Clinical information on the use of cholecalciferol in pregnancy is not available. Animal studies are inconclusive regarding effects on pregnancy/and-or/embryonic/fetal development/and-or/ partum/and-or/postnatal development (see section 5.3). The potential risk for humans is unknown.

DEVIT-3 should not be used during pregnancy unless necessary.

Lactation
Vitamin D and its metabolites are excreted in breast milk. No overdose cases have been observed in infants induced by nursing mothers taking cholecalciferol; however, there is a risk of hypercalcemia in infants of nursing mothers who receive pharmacological doses of vitamin D. When prescribing additional vitamin D to a breast-fed child, the practitioner should consider the dose of any additional vitamin D given to the mother.

Reproductive ability / Fertility
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 has no known side effects that are likely to affect the ability to drive and use or operate 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

Overdose can lead to hypervitaminosis D. An excess of vitamin D causes abnormally high levels of calcium in the blood, which can eventually cause serious damage to the soft tissues and kidneys. Tolerable upper intake level for vitamin D_3 (colecalciferol) is set at 4000 IU (100 mcg) per day. Vitamin D_3 should not be confused with its active metabolites

Acute or chronic overdose of cholecalciferol may increase the concentration of calcium in the urine and serum. Symptoms of hypercalcemia are not very clear and symptoms include nausea, vomiting, often early diarrhea followed by constipation, thirst, abdominal pain, mental disorders, bone pain, anorexia, fatigue, headache, muscle and joint pain, muscle weakness, polydipsia, polyuria, kidney stones. formation, nephrocalcinosis, renal failure, calcification in soft tissues, ECG changes, arrhythmia and pancreatitis. There have been reports of rare and isolated cases of fatal hypercalcemia.

High levels of calcium in the blood can cause permanent and irreversible renal damage and soft tissue calcification.

Treatment
Normalization of hypercalcemia due to vitamin D intoxication takes several weeks. For the treatment of hypercalcemia, it is recommended to discontinue vitamin D treatment, avoid vitamin D intake such as vitamin D supplements, dietary intake of vitamin D, Vitamin D intake and avoid sunlight. A low-calcium or no-calcium diet can also be considered.

For treatment of hypercalcemia; treatment with thiazide diuretics, lithium, vitamin A and cardiac glycosides should also be discontinued. Depending on rehydration and severity, treatment with loop diuretics, bisphosphonates, calcitonin, and corticosteroids should be considered, either alone or in combination. In addition, patients' serum electrolytes, renal functions and diuresis should be monitored. In severe cases, ECG and CVP should be monitored.

Phosphate infusions should not be administered to lower hypercalcemia of hypervitaminosis D because of the dangers of metastatic calcification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Cholecalciferol is produced in the skin under the influence of UV light, such as sunlight. In its biologically active form, cholecalciferol stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. Vitamin D_3 administration prevents the development of rickets in children and osteomalacia in adults. In the small intestine it promotes rapid and delayed calcium uptake, and it also stimulates the passive and active transport of phosphate. 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 vitamin D_3.

In addition to bone and intestinal mucosa, many other tissues have vitamin D receptors to which calcitriol, the active hormonal form of vitamin D, binds.

5.2 Pharmacokinetic properties

General particulars
The pharmacokinetics of cholecalciferol have been well studied and well known.

Absorption
Cholecalciferol is readily absorbed from the small intestine. Taking vitamin D with food potentially increases its absorption. Colecalciferol from nutritional sources is almost completely absorbed from within the gastro-intestinal tract in the presence of dietary lipids and bile acids.

Distribution
Cholecalciferol is stored in fat cells and has a biological half-life of approximately 50 days.

Biotransformation
Colecalciferol is metabolised by microsomal hydroxylase to form 25-hydroxycolecalciferol ($25(OH)D_3$, calcidiol), the primary storage form of vitamin D_3. $25(OH)D_3$ undergoes a secondary hydroxylation within the kidney to form the predominant active metabolite 1,25-hydroxycolecalciferol ($1,25(OH)_2D_3$, calcitriol). The metabolites circulate in the blood bound to a specific α-globin.

Elimination
After a single oral dose of colecalciferol, the maximum serum concentrations of the primary storage form are reached after approximately 7 days. $25(OH)D_3$ is then slowly eliminated with an apparent half-life in serum of about 50 days. Colecalciferol and its metabolites are excreted mainly in the bile and feces.

After high doses of colecalciferol, serum concentrations of $25(OH)D_3$ may be increased for months. Overdose-induced hypercalcemia may persist for weeks (see Section 4.9).

5.3 Preclinical safety data

Colecalciferol is well known and established product and has been used in clinical practice for many years. No further specific toxicological hazard for humans is expected other than in chronic overdosage where hypercalcaemia could be seen.

Teratogenicity has been observed in animal studies at doses much higher than the human therapeutic dose range. There is no further information available besides the information given in other parts of the SPC (see Section 4.6 and 4.9).

Colecalciferol overdosage in animals has been shown to induce malformations in rats, mice and rabbits at doses significantly higher than the human dose. The malformations included skeletal defects, microcephaly and cardiac malformations.

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
FD&C Yellow No:5

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.

6.5 Nature and contents of packaging

As the primary packaging material of DEVIT-3 1,000 IU Soft Capsules, blisters consisting of opaque PVC / Aclar and aluminum foil is used.
Supplied as 4 blisters (25 capsules in each blister) of 100 capsules in total, and a patient leaflet, all 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)

2021/252

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 18.08.2021
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT