SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEVIT-3 50.000 IU/ 15 ml Oral Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 ml oral drops contain
Active substance:
Vitamin D_3 (obtained from lanolin from sheep wool) 1.25 mg = 50.000 IU

Excipient(s):
Butylated hydroxyanisole 1.5 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops
Yellow, oily solution with characteristic odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
DEVIT-3 is indicated in treatment of vitamin D deficiency, maintenance and prophylaxis.

4.2 Posology and method of administration

Posology/frequency and duration of administration
1 ml of DEVIT-3 solution is 25 drops.
Your doctor will decide how you will use this medicine, follow his/her instructions.

Age group	Prevention treatment/ Long term treatment Recommended dosage	Vitamin D Deficiency treatment dosage		Maximum tolerated dosage for Long term treatment and prevention treatment in risk groups
		Daily treatment**	Weekly administration	
Newborn	400 IU/day (10 µg/day)	1000 IU/day (25 µg/day)	No	1000 IU/day (25 µg/day)
1 month – 1 year	400 IU/day (10 µg/day)	2000-3000 IU/day 50-75 µg/day)	No	1500 IU/day (37,5 µg/day)
1-10 years	400-800* IU/day (10-20 µg/day)	3000-5000 IU/day (75-125 µg/day)	No	2000 IU/day (50 µg/day)
11-18 years	400-800* IU/day (10-20 µg/day)	3000-5000 IU/day (75-125 µg/day)	No	4000 IU/day (100 µg/day)
Adults over 18 years	600-1500 IU/day (15-37,5 µg/day)	7000-10.000 IU/day (175-250 µg/day)	50.000 IU/week (1250 µg/week)***	4000 IU/day (100 µg/day)

** Can be increased to 1000 IU.*
*** Can be used 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 Vitamin D at once is not recommended.*

Routine usage of vitamin D-containing medicines during pregnancy is not recommended, however when required, it should be used under observation.

The maximum dosage of vitamin D-containing medicines used for prophylaxis in pregnancy should not exceed 1000 IU/day.

Method of Administration:
DEVIT-3 is administered via oral route.
Oral route is preferred for breast-fed children or for patients to whom injection cannot be administered. For breast-fed children, it can be administered mixed with nutrition.

Additional information on special populations

Hepatic insufficiency
No data is available.

Renal insufficiency
It should not be used in combination with calcium in patients with severe renal impairment.

Pediatric population
It is administered as indicated in the section "Posology/frequency and duration of administration".

Geriatric population
No data is available.

4.3 Contraindications
DEVIT-3 is contraindicated in patients with hypersensitivity to vitamin D or any of its excipients.
It is contraindicated for use at high doses for long period of time in severe hypertension, severe arteriosclerosis and active pulmonary tuberculosis.
It is contraindicated in cases of vitamin D hypervitaminosis, hypercalcemia, hypercalciuria, and in patients with calcium-containing kidney stone and also in calcium hypersensitivity.

4.4 Special warnings and precautions for use
A special caution is appropriate with patients
- Whose mobility is restricted
- Who are treated with benzothiadiazine derivatives
- With a history of kidney stones
- With sarcoidosis
- With pseudohypoparathyroidism

If DEVIT-3 is given together with other vitamin D_3 containing products, the total dose of vitamin D should be considered. Vitamin D is fat soluble and may accumulate in the body. This may cause toxic effects in case of overdose and long term treatment with excessive doses.
At high doses of vitamin D_3, the serum calcium levels should be monitored and particular caution is advised for these patients.

Vitamin D_3 should be used with caution in patients with impairment of renal function 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 insufficiency, vitamin D in the form of cholecalciferol is not metabolized normally and another form of vitamin D may therefore be needed.

The calcium levels in serum and urine should be monitored, and the kidney function should be checked by measuring the serum creatinine during a long-term therapy every 3 to 6 months. This check is particularly important in older patients and at a simultaneous therapy with cardiac glycosides or diuretics. In the case of hypercalcemia or symptoms of a reduced kidney function the dosage must be reduced or the therapy interrupted.

The active metabolite of vitamin D_3 (1,25-dihydroxycholecalciferol) may affect the phosphate balance. Therefore, in conditions with increased phosphate levels, treatment with a phosphate binder may be considered.

Vitamin D_3 should be prescribed with caution to patients suffering from sarcoidosis or other granulomatous disorders, due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to calcium content in serum and urine.

Vitamin D has a relatively low therapeutic index in infants and children. If hypercalcemia lasts for a long period of time, it causes mental and physical retardation in infants. There is risk of hypercalcemia in infants of breast-feeding mothers who take Vitamin D at pharmacological dose.

The highest tolerated dose for maintenance treatment and prophylaxis of risk group is 4000 IU/day (100 for µg/day) for children older than 11-years-old and adults.

DEVIT-3 contains butyl hydroxyanisole; however, it is not expected to exert any effect due to its method of administration.

4.5 Interaction with other medicinal products and other forms of interaction

Anticonvulsants, hydantoin, rifampicin, barbiturates or pyrimidon may decrease Vitamin D action due to hepatic microsomal enzyme induction.
Concurrent use with vitamin D may antagonize calcitonin, etidronat, gallium nitrate, pamidronate or plicamycin in the treatment of hypercalcemia.
Simultaneous administration of calcium-containing preparations in high doses or diuretics and thiazides increases the risk of hypercalcemia; however, it may be therapeutically advantageous in elderly and high-risk groups when it is necessary to prescribe vitamin D together with calcium; careful monitoring of serum calcium concentrations is essential during long-term therapy.
Concurrent use of vitamin D with other drugs containing vitamin D or its derivatives is not recommended because of increased potential for toxicity.
Isoniazid may reduce the efficacy of vitamin D_3 due to inhibition of the metabolic activation of vitamin D.
Patients treated with cardiac glycosides may be susceptible to high calcium levels and therefore ECG parameters and calcium levels of these patients must be absolutely monitored.
Drugs leading to fat malabsorption, e.g. orlistat and colestyramin, may impair the absorption of vitamin D.

Additional information on special populations
No interaction study is available.

Pediatric population
No interaction study is available.

4.6 Fertility, pregnancy and lactation

General principles
Pregnancy category is C

Women of child-bearing potential/Contraception
No data is available on contraception.

Pregnancy
No clinical information is available on administration of cholecalciferol during pregnancy.
Animal studies do not indicate effects with respect to pregnancy/and-or/embryonal/fetal development/and-or/parturition/and-or/postnatal development. Potential risk to humans is unknown. Unless it is necessary, DEVIT-3 should not be used during pregnancy.

Routine usage of vitamin D-containing medicines during pregnancy is not recommended, however when required, it should be used under observation.

The maximum dosage of vitamin D-containing medicines used for prophylaxis in pregnancy should not exceed 1000 IU/day.

Breast-feeding
Only small amounts of vitamin D metabolites appear in human milk. Infants who are totally breast-fed and have little exposure to the sun may require vitamin D supplementation.

Fertility
It does not have any known effect.

4.7 Effects on ability to drive and use machinery
It does not have any known effect.

4.8 Undesirable effects
Undesirable effects are based on the following frequencies according to system-organ class:
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), unknown (cannot be estimated based on the available data)

The frequency of undesirable effects is unknown due to the nonexisting of extensive clinical trials.

The possibility of side effects of DEVIT-3 taking is low in routine doses and durations. Undesirable effects given below can be developed when vitamin D_3 given at high doses and prolongation of duration of administration.

Metabolism and nutritional disorders
Unknown: Hypercalciuria, hypercalcemia and increased amount of residual nitrogen in blood.

Gastrointestinal disorders
Unknown: Constipation, flatulence, nausea, abdominal pain, diarrhea

Skin and subcutaneous tissue disorders
Unknown: Hypersensitivity reactions such as pruritus, rash, urticaria

Renal and urinary tract diseases
Unknown: Polyuria, polydipsia, anuria

General disorders and administration site conditions
Unknown: Fever

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 to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose

Symptoms:
Acute and chronic overdose of vitamin D leads to hypercalcemia. Symptoms of hypercalcemia are tiredness, psychiatric symptoms (such as euphoria, dazedness, disturbed consciousness), nausea, vomiting, lack of appetite, weight loss, thirst, polyuria, formation of renal calculi, nephrocalcinosis, extraosseous calcification in bones and kidney failure, changes in ECG, arrhythmias and pancreatitis.
In isolated cases their course has been described as fatal.

Overdose in pregnancy:
Massive doses during pregnancy have been related to the occurrence of aortic stenosis syndrome and idiopathic hypercalcemia in newborns. In addition, anomalies of the face, physical and mental retardation, strabism, enamel defects, craniosynostosis, supervalvular aortic stenosis, pulmonary stenosis, inguinal hernia, cryptorchidism in male progeny, as well as premature development of secondary sex characteristics in female progeny have been reported.
However, some case reports are available to the effect that normal children were born to mothers with hypoparathyroidism, receiving very high doses.

Treatment:
Treatment of vitamin D analog intoxication consists of withdrawal of the vitamin D and calcium supplements, maintenance of a low-calcium diet, administration of oral or IV fluids. If needed, calciuric diuretics (e.g., furosemide and ethacrynic acid) to decrease serum calcium concentrations. Hemodialysis or peritoneal dialysis with a calcium-free dialysate may also be used. If ingestion is recent, gastric lavage or emesis may prevent further absorption. Hypercalcemia can last for 2 or more months following chronic administration of excessive doses of these drugs.
If a massive dose has been ingested ventricular emptying should be considered, together with administration of carbon. Sun light and further administration of vitamin D should be avoided.

Rehydration and treatment with diuretics, e.g. furosemide may be applied to ensure adequate diuresis. In hypercalcemia, biphosphonates or calcitonin and corticosteroids may be given. The treatment is directed to symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and its analogues
ATC code: A11CC05

Cholecalciferol (Vitamin D_3) increases serum phosphate and calcium concentrations in human essentially by increasing their absorption. It provides calcification of bone. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular reabsorption. Along with parathyroid hormone, it regulates calcium and phosphorus concentrations to remain at normal levels. Cholecalciferol also stimulates bone resorption and it is required for normal mineralization of bone. Parathyroid hormone (PTH) secretion is inhibited indirectly by the increased calcium uptake in the small intestine. Normal requirement of body is between 400 and 800 IU per day.

5.2 Pharmacokinetic properties

General properties

Absorption:
Cholecalciferol is well absorbed from the gastrointestinal tract.

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. Cholecalciferol has a slow onset and a long duration of action. Its half-life is 19-25 hours.

Biotransformation:
Vitamin D is converted to 25-hydroxy derivative in mitochondria in the liver by the enzyme 25-hydroxylase. This metabolite is hydroxylated in the kidneys once again by the enzyme vitamin D 1-α hydroxylase and activated. When 1-25 hydroxylated metabolite concentration reaches the sufficient level, it is converted in the kidneys to its metabolite with biological activity at minimal level and with 24, 25 hydroxyl.

Elimination:
Vitamin D compounds and their metabolites are excreted mainly in the bile and feces. It is excreted in urine with small amounts. Main metabolite excreted in urine is calcitroic acid.

Linearity/Non-Linearity:
No study is available.

5.3 Preclinical safety data

Chronic safety evaluation studies in animals show that Vitamin D and Calcium combination is generally well tolerated. However, Vitamin D_3 overdosage during pregnancy induced malformation in rats, mice and rabbits (skeletal defects, microcephaly, cardiac malformation).
Animal studies do not indicate effects with respect to pregnancy/and-or/embryonal/fetal development/and-or/parturition/and-or/postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Butylated hydroxyanisole
Sunflower seed oil

6.2. Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Keep at room temperature below 25°C as tightly capped and away from light.

6.5 Nature and contents of packaging
Amber-colored, screwed top glass bottle of 20 ml, central dropper made of low-density PE and screwed cap made of white opaque PP with safety ring.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER

70/11

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 22.08.1963
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

19.11.2020