SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEVIT-3 300.000 IU/ml Solution for IM Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains
Active substance:
Vitamin D_3 (obtained from lanolin from sheep wool) 7.5 mg (300.000 IU)

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

3. PHARMACEUTICAL FORM

Light yellow-colored, oily solution with characteristic (oily) odor in colored ampoules (Type I) of 1 ml.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
DEVIT-3 is indicated for vitamin D deficiency only in patients with gastrointestinal tract absorption disorders.

4.2 Posology and method of administration

Posology
Dose and duration of treatment are determined on doctor's advice according to the disease to be treated. Patients should use according to doctors' advice.

Frequency and duration of administration
The doctor will decide how to use the drug. It should be used according to the doctor's advice.

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	4000 IU/day (100 µg/day)

			µg/week)***	

** 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 can be administered via intramuscular route. It must be injected into the muscle in calcium malabsorption.

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
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- hypercalcemia and/or hypercalciuria
- pregnancy and lactation

4.4 Special warnings and precautions for use
DEVIT-3 should not be administered in following conditions:
- Patients with a tendency to form calcium containing kidney stones in the anamnesis;
- Patients with pseudohypoparathyroidism (long-lasting overdoses may cause temporarily normal dose vitamin D sensitivity, which may reduce demand (or need) of vitamin D). Easily controllable vitamin D derivatives should be used in these cases.

DEVIT-3 should be administered only with caution following conditions:
- Patients with impaired renal calcium and phosphate excretion, in case of treatment with benzothiadiazine derivatives and immobilized patients, e.g. due to a cast (risk of hypercalcemia, hypercalciuria);
- Patients suffering from sarcoidosis because the risk of transformation of vitamin D into its active metabolites is increased.

The calcium levels in serum and urine should be monitored in these patients.

During a long-term therapy with DEVIT-3 the calcium levels in serum and urine should be monitored every 3 to 6 months, and the kidney function should be checked by measuring the serum creatinine. This check is particularly important in older patients and during a concomitant therapy with cardiac glycosides or diuretics. In case of hypercalcemia or symptoms of an impaired kidney function the dosage must be reduced or the therapy be postponed. It is recommended to reduce the dosage or to interrupt the therapy if the calcium level in the urine exceeds 7.5 mmol/24 hours (300 mg/24 hours).

If other drugs containing vitamin D are prescribed, the dosage of vitamin D from DEVIT-3 must be taken into account. Additional administration of vitamin D or calcium should only be carried out under medical supervision. In such cases the calcium levels in serum and urine must be monitored.

In patients with renal insufficiency, that are treated with DEVIT-3, the effect on the calcium and phosphate level should be monitored.

In pregnant women, if required, it can be used at a proper dose according to doctor's advice. 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.

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 as well as congenital heart and eye diseases 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.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoine or barbiturates can reduce the effect of vitamin D3.

Thiazide diuretics can lead to hypercalcemia due to the reduction of the renal calcium excretion. Therefore, the calcium levels in serum and urine should be monitored during a long-term therapy.

The simultaneous administration of glucocorticoids can reduce the effect of vitamin D3.

Isoniazid may reduce the effectiveness of vitamin D_3 due to inhibition of the metabolic activation of vitamin D.

The toxicity of cardiac glycosides may be raised due to an increase of the calcium level during the therapy with vitamin D (risk of cardiac dysrhythmia). In these patients ECG and calcium level in serum and urine should be monitored.

Only in exceptional cases and under serum calcium controls DEVIT-3 should be combined with metabolic products or analogues 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
Overdose of vitamin D in pregnancy must be prevented since long-lasting hypercalcemia can lead to physical and mental retardation as well as to congenital heart and eye diseases of the child.

Therefore DEVIT-3 is contraindicated during pregnancy. If a vitamin D supplement should be required, a drug with a lower cholecalciferol content than DEVIT-3 should be chosen.

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
DEVIT-3 is contraindicated during lactation. If a vitamin D supplement should be required, a drug with a lower cholecalciferol content than DEVIT-3 should be chosen.

Fertility
It does not have any known effect.

4.7 Effects on ability to drive and use machinery
No studies on the effects on the ability to drive and to use machines have been performed.

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 side effects of vitamin D result from hypercalcemia due to overdose.

Metabolism and nutritional disorders
Unknown: Hypercalciuria, hypercalcemia

Nervous System Disorders
Unknown: Psychic symptoms, impaired consciousness

Cardiac diseases
Unknown: Arrhythmias

Gastrointestinal disorders
Unknown: Nausea, vomiting, anorexia, weight loss

Renal and urinary tract diseases
Unknown: Polyuria, anuria, polydipsia, kidney stone formation, nephrocalcinosis, excessive calcification.

Skin and subcutaneous tissue disorders
Unknown: Hypersensitivity reactions such as 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 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 of overdose
Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) have a relative low therapeutic index. In adults with normal parathyroid function the threshold for vitamin D intoxication is between 40.000 and 100.000 IU per day during 1 to 2 months. Babies and infants may react severely to far lower concentrations. Therefore vitamin D should not be administered without medical control.
Overdose leads to an increase of phosphorus in serum and urine and to the hypercalcemia syndrome, later also to calcium deposit in the tissues, primarily in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.
The symptoms of an intoxication are nonspecific and may appear as nausea, vomiting, at first often as diarrhea, later on as obstipation, anorexia, weakness, headache, muscle and joint pain, muscle weakness as well as persistent drowsiness, azotaemia, polydipsia and polyuria, finally as exsiccosis. Typical laboratory test results are hypercalcemia, hypercalciuria as well as increased serum levels of 25-hydroxycholecalciferol.

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 of overdose
In case of an overdose measures for the treatment of the often long-lasting and potentially threatening hypercalcemia are required.
The first measure is to stop the administration of the vitamin D product; a normalization of the hypercalcemia due to vitamin D intoxication lasts for several weeks.

Graduated according to the extent of the hypercalcemia low calcium or calcium free nutrition, plenty intake of fluids, forced diuresis by means of furosemide as well as the administration of glucocorticoids and calcitonine may be applied.
Infusions of isotonic NaCl solution (3-6 l in 24 hour) with addition of furosemide as well as possibly 15 mg/kg BW sodium edetate under continuous calcium and ECG-control have a quite reliable calcium lowering effect in patients with a sufficient kidney function. Hemodialysis (calcium free dialysis fluid) is indicated in case of oligouria.
A special antidote does not exist.
It is recommended to inform patients with long-term treatment with higher vitamin D doses about the symptoms of a possible overdose (nausea, vomiting, at the beginning often diarrheas, later obstipation, anorexia, weakness, headache, muscle and joint pain, muscle weakness, drowsiness, azotaemia, polydipsia and polyuria).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Cholecalciferol (vitamin D3) is synthesized in the skin under the influence of UV rays and is then metabolized in two hydroxylation steps, at first in the liver (position 25) and next in the kidney tissue (position 1) into the biologically active form 1,25-dihydroxy-cholecalciferol. 1,25-dihydroxy-cholecalciferol is essentially involved in the regulation of the calcium and phosphate balance together with parathyroid hormone and calcitonine. In case of a vitamin D deficiency the calcification of the skeleton does not occur (rickets) or bone decalcification may result (osteomalacia).
According to the formation, physiological regulation and mode of action the so-called vitamin D3 is to be considered as precursor of a steroid hormone. Besides the physiological production in the skin cholecalciferol can be supplied with nutrition or as drug product. When administered as a drug product the physiological inhibition of the cutaneous vitamin D synthesis will be avoided and overdoses and intoxications may occur. Ergocalciferol (vitamin D2) is formed in plants. In humans it is metabolically activated like cholecalciferol and has qualitatively and quantitatively similar effects.

Occurrence and coverage of need
Fish liver oil and fish are particularly rich in vitamin D, small quantities are found in meat, egg yolk, milk, dairy products and avocado.
The daily demand for adults is 5 µg, corresponding to 200 IU. Healthy adults can cover their vitamin D requirements at sufficient sun exposure by own synthesis. The supply by food is only of minor importance. However, it can be important in critical conditions (climate, way of life).

Deficiency symptoms
Deficiency symptoms may appear for instance in immature premature babies, in infants exclusively breastfed for more than six months without supplementary food containing calcium, and in children on strict vegetarian diet. The rare vitamin D deficiency in adults may be caused by inadequate alimentary supply, insufficient UV exposure, malabsorption and maldigestion, hepatocirrhosis as well as renal insufficiency.

5.2 Pharmacokinetic properties

General properties

Absorption:

In alimentary doses vitamin D is almost completely absorbed from the nutrition together with nutrition lipids and bile acids. Higher doses are absorbed with a resorption rate of about 2/3. In the skin vitamin D is synthesized under the influence of UV light from 7-dehydrocholesterol.

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:

By means of a specific transport protein vitamin D reaches the liver where it is metabolized by a microsomal hydroxylase to 25-hydroxy-cholecalciferol. 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:

The excretion of vitamin D and its metabolites is carried out biliary/fecal.
Vitamin D is stored in fatty tissue and has therefore a long biological half-life. After high vitamin D doses the 25-hydroxyvitamin D concentrations in serum can be increased for months. Hypercalcemia caused by overdose can persist for weeks (see section 4.9).

5.3 Preclinical safety data

There are no further special toxicological risks to humans apart from these listed under the sections 4.6 and 4.9.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene
Sunflower seed oil

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at room temperature below 25°C.
Store in a dry place and protect from light. Keep in its original package.

6.5 Nature and contents of packaging

Amber-colored, printed ampoules of 1 ml made of Type I glass.
Each box contains 1, 50 or 100 ampoules of 1 ml.

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

61/84

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 09.12.1961
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

12.11.2020