SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DESIFEROL 50.000 IU/15 ml oral drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle (15 ml) contains

Active substance(s):

Vitamin D_3 (obtained from sheep wool) 50.000 IU

Excipient(s):

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Drops
Yellowish, clear, particle-free oily solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

It is indicated for the treatment, maintenance and prophylaxis of vitamin D deficiency.

4.2. Posology and method of administration

Posology/Frequency of administration and duration of the treatment:
One ml DESIFEROL solution consists of 25 drops.
Your doctor will decide how to use the drug. Use according to your doctor's advice.

Age Group	**Proposed Dose for Prevention / Maintenance**		**Treatment Dosage for Vitamin D Deficiency**			**Maximum Tolerated Dose for Maintenance and Prevention in Groups At Risk**	
			Daily treatment **		**Weekly treatment**		
Newborn	400 IU/day (10 µg/ day)	3 drops	1000 IU/ day (25 µg/ day)	8 drops	No	1000 IU/ day (25 µg/ day)	8 drops
1 month-1 year	400 IU/ day (10 µg/ day)	3 drops	2000-3000 IU/ day (50-75 µg/ day)	15 - 23 drops	No	1500 IU/ day (37.5 µg/ day)	11 drops
1-10 years	400-800* IU/day (10-20 µg/ day)	3-6 drops	3000-5000 IU/ day (75-125 µg/ day)	23 - 38 drops	No	2000 IU/ day (50 µg/ day)	15 drops
11-18 years	400-800* IU/day (10-20 µg/ day)	3-6 drops	3000-5000 IU/ day (75-125 µg/ day)	23 - 38 drops	No	4000 IU/ day (100 µg/ day)	30 drops
Adults over the age of 18	600-1500 IU/ day (15-37.5 µg/ day)	5-11 drops	7000-10.000 IU/ day (175-250 µg/ day)	53 - 75 drops	50.000 IU/week (1250 µg/week)***	4000 IU/ day (100 µg/ day)	30 drops

** If necessary, it can be increased up to 1000 IU.*

*** It can be used up to 6-8 weeks.*

**** If it is desired to apply a weekly dose instead of daily, the dose of 50,000 IU can be used as a weekly dose at a single time (1 bottle) up to 6-8 weeks. It is not recommended to use more than 50,000 IU of vitamin D at a time.*

Although routine use of drugs containing vitamin D is not recommended during pregnancy, it can be used under the control of a doctor if necessary.

In the use of drugs containing vitamin D for prevention during pregnancy, the maximum dose should not exceed 1000 IU / day.

Method of administration:
DESIFEROL is administered via oral route.
Oral route is preferred in breastfed infants or in patients whose condition does not allow administration via injection. It may be added to food in breastfed infants.

Additional information for special populations:
Hepatic Failure:
No data available.

Renal Failure:
In patients with severe renal failure, it should not be used in conjunction with calcium.

Pediatric population:
It is administered as specified in the section titled “Posology/Frequency of administration and duration of the treatment:

Geriatric population:
No data available.

4.3. Contraindications

DESIFEROL is contraindicated in patients who have hypersensitivity to vitamin D or any of the ingredients.
In severe hypertension, advanced arteriosclerosis, and active pulmonary tuberculosis, prolonged use of high doses is contraindicated.
It is contraindicated in cases of hypervitaminosis D, hypercalcemia, hypercalciuria, calcareous renal stone, and hypersensitivity to calcium.

4.4. Special warnings and precautions for use

The following populations are at high risk for vitamin D deficiency. The maximum tolerated dose for the prophylaxis of these populations is given in the section "4.2 Posology and method of administration" and below, according to age groups.

- Patients requiring care or inpatient
- Patients with dark skin color
- People who are not sufficiently exposed to the sun or use sunscreen continuously
- Patients evaluated for osteoporosis
- Obese patients
- Simultaneous use of some drugs (e.g. anticonvulsant drugs, glucocorticoids, anti-retrovirals)
- Patients recently treated for vitamin D deficiency and require maintenance therapy
- Patients with liver or kidney disease
- Patients with malabsorption, inflammatory bowel disease, and celiac disease
- In support of the specific treatment of osteoporosis: 8 drops per day (1000 IU)

The maximum tolerated dose for the prophylaxis of groups at risk:

Age Group	Maximum Tolerated Dose (IU/day)	Maximum Tolerated Drops/day
Newborn	1000 IU/day (25 µg/day)	8 drops/day
1 month-1 year	1500 IU/day (37,5 µg/day)	11 drops /day
1-10 years	2000 IU/day (50 µg/day)	15 drops /day
11-18 years	4000 IU/day (100 µg/day)	30 drops /day
Adults over the age of 18	4000 IU/day (100 µg/day)	30 drops /day

Although routine use of drugs containing vitamin D is not recommended during pregnancy, it should be used under the supervision of a physician when necessary.

When using drugs containing vitamin D for prophylaxis during pregnancy, the maximum dose should not exceed 1000 IU / day (8 drops per day).

A special warning should be made for the following patients;
- Restricted mobility
- Treatment with benzothiadiazine derivatives
- History of nephrolithiasis.
- Sarcoidosis
- Pseudo-hypoparathyroidism

If DESIFEROL is to be given with other vitamin D_3 containing products, careful consideration of the overall dose of vitamin D is necessary. Vitamin D is fat-soluble and may accumulate in the body. This may cause toxic effects in overdose and in prolonged treatment with excessive doses.

When administering high doses of vitamin D_3 in patients with a history of nephrolithiasis, monitoring of serum calcium values can be considered and special caution is recommended in such patients.

In patients with impaired renal function, vitamin D_3 should be used cautiously and such patients should necessarily be monitored for their levels of calcium and phosphate. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D, in the form of cholecalciferol, normally is not metabolized and therefore another form of vitamin D may be needed.

In prolonged treatment, serum and urine levels of calcium, and serum levels of creatinine should be measured and renal functions must necessarily be monitored every 3 to 6 months. This is especially important in concomitant treatment with cardiac glycosides or diuretics in elderly patients.

Symptoms of hypercalcemia or impaired renal function require dose reduction or discontinuation of treatment.

The active metabolite (1,25-dihydroxycholecalciferol) of Vitamin D3 may affect phosphate balance. Therefore, in case of increased level of phosphate, treatment with phosphate-binding agents should be considered.

Vitamin D_3 should be cautiously administered in patients with sarcoidosis and other granulomatous diseases due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored for their serum and urine calcium levels.

Vitamin D has a very low therapeutic index in infants and children. Prolonged hypercalcemia in infants leads to retarded physical and mental development. Infants to nursing mothers receiving vitamin D at pharmacologic dosage are at risk of hypercalcemia.

4.5 Interactions with other medicinal products and other forms of interactions

Concomitant use with hepatic microsomal enzyme inducing anticonvulsants, hydantoin, rifampicin, barbiturates or pyrimidine may decrease the activity of vitamin D.

Concomitant use with calcitonin, etidronate, gallium nitrate, pamidronate or plicamycin in hypercalcemia treatment antagonizes them.

Concomitant administration of drugs containing high doses of calcium or diuretics, and of thiazide, increases the risk of hypercalcemia. However, this may be an advantage for elderly and for patients in the high-risk groups, in which concomitant use of vitamin D and calcium is required. In such prolonged treatments, careful monitoring of serum calcium concentrations is necessary.

Concomitant use with other products containing vitamin D, or its analogues is not recommended due to increased risk of toxicity.

Isoniazid may reduce the effectiveness 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 should have their ECG parameters and calcium levels monitored.

Medicinal products that lead to fat malabsorption, such as orlistat and cholestyramine, may reduce the absorption of vitamin D.

Additional information for special populations:

No interaction study available.

Pediatric population:

No interaction study available.

4.6. Fertility, pregnancy and lactation

General advice:

Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)

There is no data on birth control.

Pregnancy

There is no clinical data regarding the use of cholecalciferol during pregnancy. Studies on animals regarding pregnancy/and-or/ embryonal/fetal growth /and-or/ perinatal /and or/ postnatal growth are insufficient. Potential risk for human is not known

Although routine use of DESİFEROL is not recommended during pregnancy, it can be used under the control of a doctor, if necessary.

When using drugs containing vitamin D for prophylaxis during pregnancy, the maximum dose should not exceed 1000 IU / day (8 drops per day).

Lactation
Vitamin D metabolites are observed in small amounts in breast milk in human. Exclusively breastfed infants and infants receiving inadequate sunlight exposure may require vitamin D supplement.

Reproduction/ Fertility
No known side effect.

4.7 Effects on ability to drive and use of machines
No known side effect.

4.8 Undesirable effects
Reported undesirable effects are classified as follows:
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 data available).

Frequencies of adverse reactions are not known, as no larger clinical trials have been conducted.

DESIFEROL in normal doses and duration of treatment rarely has side effects. Administration of vitamin D3 at high doses and extending the duration of treatment in an uncontrolled manner may lead to following effects.

Metabolism and nutrition disorders
Unknown: Hypercalciuria, hypercalcemia and increased residual nitrogen in the blood.

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

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

Renal and urinary disorders
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 via Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose and treatment

Symptoms

Acute or chronic overdose of vitamin D causes hypercalcemia. Symptoms of hypercalcemia include tiredness, psychiatric symptoms (e.g., euphoria, dizziness, and confusion), nausea, vomiting, anorexia, weight loss, thirst, polyuria, and kidney stone formation, nephrocalcinosis, osseous calcification and kidney failure, changes in ECG, arrhythmia, and pancreatitis.

In isolated cases, the course of these side effects has been defined as fatal.

Overdose in pregnancy:
Massive doses during pregnancy have been related to aortic stenosis syndrome and idiopathic hypercalcemia in newborns. In addition, anomalies of the face, retardation in physical and mental development, strabismus, enamel defects, craniosynostosis, supravalvular 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, several cases of normal newborns born to mothers with hypoparathyroidism using high doses of vitamin D have been reported.

Treatment

In cases of intoxications due to analogues of vitamin D, supplement with vitamin D and calcium is discontinued, low-calcium diet is implemented, and i.v. fluid is given.
When necessary, serum calcium concentrations can be reduced by administration of calciuric diuretics (e.g. furosemide and etacrynic acid). Hemodialysis or peritoneal dialysis can also be used against calcium-free dialysates. When vitamin D ingestion is recent, gastric lavage or regurgitation can be applied to prevent further absorption. Hypercalcemia induced by chronic overdose of cholecalciferol can be terminated in a period of 2 months or longer.

In case of massive dose, ventricular ejection should be considered along with active carbon administration. Exposure to sunlight should be avoided and administration of vitamin D should be discontinued. To provide sufficient diuresis, rehydration and treatment with diuretic agents like furosemide should be applied. In cases of hypercalcemia, administration of biphosphonates or calcitonin, and corticosteroids can be considered. Treatment is symptomatic.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and its analogues

ATC Code: A11CC05

Cholecalciferol (Vitamin D_3) increases serum phosphate and calcium concentrations, mainly through increasing their absorption. It allows calcium formation in bones. It increases reabsorption of calcium and phosphate through tubular cells, thus reduces the elimination of calcium and phosphate. Cholecalciferol ensures normalized calcium and phosphate levels along with parathyroid hormone. Cholecalciferol also stimulates bone reabsorption and is crucial for normal bone mineralization. Cholecalciferol at physiological doses also increases resorption of calcium by the kidneys. It inhibits parathyroid hormone (PTH) secretion through intestinal residual calcium absorption. The normal daily requirement of the body is 400-800 I.U.

5.2 Pharmacokinetic properties

General characteristics

Absorption:
Cholecalciferol is well absorbed in gastrointestinal tract.

Distribution:
Vitamin D and its metabolites in blood bind to a specific a-globulin. Vitamin D is stored in adipose tissues and muscles for a long time and slowly released from these storage sites. Cholecalciferol has a long-term activity despite a slow start. Half-life is 19 to 25 hours.

Biotransformation:
Cholecalciferol is converted to 25-hydroxy derivative in the liver by the mitochondrial 25-hydroxylase enzyme. This metabolite is further hydroxylated in the kidneys by vitamin D 1-α hydroxylase enzyme and become activated. When 1-25 hydroxylated metabolite concentration reaches to an optimal level in the kidney, it is converted to 24, 25 hydroxylated metabolite with minimal biological activity.

Elimination:
Vitamin D compounds and its metabolites are mainly excreted through the bile into the feces. Little amounts are eliminated through the urine. The major metabolite eliminated through the urine is calcitroic acid.

Linearity/Non-linearity:
No study available.

5.3. Preclinical safety data
Overdose of vitamin D_3 during pregnancy in mice, rats, and rabbits caused to malformation (skeletal disorders, microcephalia, and cardiac malformation).

Studies on animals regarding pregnancy/and-or/ embryonal/fetal growth /and-or/ perinatal /and or/ postnatal growth are insufficient.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Butylhydroxyanisole
Sunflower oil

6.2. Incompatibilities
Not available.

6.3. Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 25°C, tightly closed, and away from light.

6.5 Nature and contents of container
DESIFEROL is marketed in amber colored glass bottles (Type III) closed with pilfer-proof HDPE closure and LDPE dropper seal in a cardboard box.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with “Directive on Control of Medical Waste” and “Directive on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

2017/512

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of the first authorization: 30.06.2017
Date of the renewal of the authorization:

10. DATE OF REVISION OF THE TEXT

07.01.2021