## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT
DESIFEROL 2000 IU film coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains;

**Active substance(s):**
Vitamin $D_3$ (obtained from sheep wool) 2000 IU (50 micrograms)

**Excipient(s)**:
Lactose monohydrate (obtained from cow milk) 120.9 mg

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM
Film Coated Tablet
Nacreous whitish color, bright, film coated, rounded tablets with notch in the middle of one side (to be divided into equal doses).

### 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**
Each film coated tablet contains 2000 IU (50 micrograms) Vitamin $D_3$. The tablets can be divided into two equal doses, thanks to the notch, and a dose of 1000 IU (25 micrograms) can be adjusted.

Your doctor will decide how to use the medicine. Use according to your doctor's advice.

| Age Group | Recommended Dose for Prophylaxis / Maintenance Treatment | Treatment Dose for Vitamin D Deficiency | | Maximum Tolerated Dose for Maintenance Treatment and Prophylaxis of Groups at Risk |
|---|---|---|---|---|
| | | Daily treatment** | Weekly tretment*** | |
| **New born** | 400 IU/day (10 mcg/day) | 1000 IU/day (25 mcg/day) | Not applicable | 1000 IU/day (25 mcg/day) |
| **1 month – 1 year old** | 400 IU/day (10 mcg/day) | 2000-3000 IU/day (50-75 mcg/day) | Not applicable | 1500 IU/day (37,5 mcg/day) |

| | | | | |
|---|---|---|---|---|
| **1-10 years old** | 400-800* IU/day (10-20 mcg/day) | 3000-5000 IU/day (75-125 mcg/day) | Not applicable | 2000 IU/day (50 mcg/day) |
| **11-18 years old** | 400-800* IU/day (10-20 mcg/day) | 3000-5000 IU/day (75-125 mcg/day) | Not applicable | 4000 IU/day (100 mcg/day) |
| **Over 18 years old** | 600-1500 IU/day (15-37,5 mcg/day) | 7000-10.000 IU/day (175-250 mcg/day) | 50.000 IU/week (1250 mcg/week)*** | 4000 IU/day (100 mcg/day) |

** If necessary, it can be increased up to 1000 IU.*
*** It can be used up to 6-8 weeks.*
**** If weekly dose is intended to be applied instead of daily dose, 50.000 IU can be used weekly up to 6-8 weeks. It is not recommended to use more than 50,000 IU of vitamin D at one time.*

Although routine use is not recommended during pregnancy, it can be used under physician control, if necessary.

Maximum dose should not be exceed 1000 IU/day, when it is used in pregnancy with the aim of prophylaxis.

**Method of administration:**
DESIFEROL is administered orally.

**Additional information for special populations:**
**Renal failure:**
It should not be used in patients with severe renal failure.

**Hepatic failure:**
Dose adjustment is not required.

**Pediatric population:**
It is not recommended to use in children aged under 12 years.
It is used as it is recommended in Posology/Frequency of administration and duration of the treatment

**Geriatric population:**
It is used as in adults.

**4.3. Contraindications**
It is contraindicated;
- in patients with hypersensitivity to the active substance or to any excipient listed in section 6.1,
- Diseases and/or conditions resulting in 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 patients with severe renal failure,
- in children under 12 years of age,
- Contraindicated in case of hypervitaminosis D.

**4.4. Special warnings and precautions for use**
DESIFEROL should be prescribed with caution in patients with sarcoidosis, a disease caused by abnormal functioning of the immune system, as it may pose a risk due to increased metabolism of conversion to the active form of vitamin D. These patients should be monitored for calcium content in serum and urine.

Caution should be exercised when used in patients undergoing treatment for cardiovascular disease (see section 4.5).

During long-term therapy, serum calcium levels should be monitored and renal function should be monitored with serum creatinine measurements. Follow-up is important, especially in elderly patients with concomitant therapy with cardiac glycosides or diuretics (see section 4.5) and in patients with a high predisposition to form kidney stones. 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.

DESIFEROL should be used with caution in patients with moderate to mild renal impairment and its effects on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be considered. In patients with severe renal impairment, vitamin D in the form of cholecalciferol is not normally metabolized. Therefore, other forms of vitamin D should be used.

The vitamin D content (2000 IU) in DESIFEROL should be considered when prescribing other medicinal products containing vitamin D. Additional doses of vitamin D should be taken under close medical supervision. In such cases, it is necessary to frequently monitor serum calcium levels and urinary calcium excretion.

The need for additional calcium supplements should be considered for each individual patient. Calcium supplements should be given under close medical supervision. In such cases, it is necessary to frequently monitor serum calcium levels and urinary calcium excretion.

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

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

DESIFEROL contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

**4.5 Interactions with other medicinal products and other forms of interaction**
Phosphate infusion should not be administered in the low hypercalcemia state of hypervitaminosis D due to the danger of metastatic calcification.

Thiazide diuretics reduce urinary excretion of calcium. Concomitant use with thiazide diuretics results in an increased risk of hypercalcemia. Therefore, serum and urine calcium should be monitored regularly during concomitant use of thiazide diuretics.

Concomitant use of phenytoin and barbiturates may reduce the effect of vitamin D as it increases the metabolic rate.

An overdose of vitamin D with digitalis or other cardiac glycosides may induce hypercalcemia because of its intropic effects, which can increase the risk of digitalis toxicity and serious arrhythmias. Electrocardiography (ECG) and serum calcium levels of the patients should be closely monitored.

Glucocorticoid steroids can increase the rate of metabolism and elimination of vitamin D. During concomitant use with glucocorticoid steroids, the dose of DESIFEROL may need to be increased.

Rifampicin may reduce the efficacy of cholecalciferol as it induces hepatic enzyme induction.

Since isoniazid inhibits the metabolic activation of cholecalciferol, it may reduce the efficacy of cholecalciferol.

Concomitant use with cholestyramine, ion exchange resins such as colestipol or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. Orlistat can potentially impair the absorption of cholecalciferol as it causes fat malabsorption.

The cytotoxic agent actinomycin and the antifungal agent imidazole affect vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme 25-hydroxyvitamin D-1-hydroxylase.

**Additional information for special populations:**
Data is not available.

**Pediatric population:**
Data is not available.

**4.6. Pregnancy and lactation**

**General advise:**
Pregnancy category: C

**Women of childbearing potential / Birth control (Contraception)**
There is no data on birth control.

**Pregnancy**
High-dose vitamin D has teratogenic effects in animal experiments. Overdose of vitamin D should be avoided during pregnancy because prolonged hypercalcemia causes physical and mental disorders (mental retardation), supravalvular aortic stenosis and eye disorders.

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

In the use of drugs containing vitamin D for prophylaxis during pregnancy, the maximum dose should not exceed 1,000 IU/day.

Animal studies have shown reproductive toxicity (see section 5.3). DESIFEROL should not be used during pregnancy unless necessary.

**Lactation**
Vitamin D3 and its metabolites pass into breast milk. No cases of overdose have been observed in newborns fed with breast milk of mothers using cholecalciferol. However, when prescribing supplemental vitamin D to breastfed children, the physician should consider the dose of vitamin D given to the mother. There is a risk of hypercalcemia in infants of breastfeeding mothers who receive pharmacological doses of vitamin D.

**Reproduction/ Fertility**
There are no data on the effect of DESIFEROL on fertility. Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

**4.7 Effects on ability to drive and use machines**
There are no data on the effect on the ability to drive or use machines. However, DESIFEROL has no known side effects that may affect the ability to drive and use machines.

**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), not known (cannot be estimated from the available data).

**Immune system diseases**
Not known: hypersensitivity reactions such as angioedema, laryngeal edema

**Metabolism and nutritional diseases**
Uncommon: Hypercalcaemia, hypercalciuria

**Skin and subcutaneous tissue diseases**
Rare: Pruritus, rash, urticaria

**4.9 Overdose and treatment**
Overdose can lead to hyper-vitaminosis 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. Vitamin D3 should not be confused with its active metabolites.

Acute and chronic overdose of cholecalciferol causes hypercalcemia, increased serum and urinary calcium concentrations.
Symptoms of hypercalcemia (increased serum and urine calcium concentrations); anorexia, thirst, nausea, vomiting, often early diarrhea followed by constipation, abdominal pain, muscle weakness, fatigue, mental disorders, polydipsia, polyuria, bone pain, nephrocalcinosis, in severe cases renal stone, kidney failure, soft tissue calcification, ECG changes , pancreatitis, cardiac arrhythmias. Excessive hypercalcemia can result in coma and death.

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

Treatment
It takes several weeks for hypercalcemia from vitamin D intoxication to return to normal. For the treatment of hypercalcemia, vitamin D therapy should be discontinued and it is recommended to avoid vitamin D supplements, another vitamin D administration such as dietary intake of vitamin D, and avoid exposure to sunlight. A low calcium or no calcium diet may also be considered. Treatment of hypercalcemia: Vitamin D treatment should be discontinued. However, 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, alone or in combination, should be considered. In addition, patients' serum electrolytes, renal functions and diuresis should be monitored. In severe cases, ECG and CVB should be monitored.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group:** Vitamin D and its analogues
ATC Code: A11CC05

Vitamin D increases the absorption of calcium and phosphate in the intestine.

Vitamin D3 administration prevents the development of rickets in children and osteomalacia in adults. It also prevents the increase of parathyroid hormone (PTH) caused by calcium deficiency, which causes increased bone resorption.

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 characteristics**

Absorption:
Cholecalciferol is easily absorbed in the small intestine. Food-derived cholecalciferol is almost completely absorbed from the gastrointestinal tract with fatty foods and bile acids.

Distribution:
Vitamin D and its metabolites in the blood are bind to a specific alpha-globulin. Cholecalciferol is stored in adipose tissues and muscles for a long time and slowly released from these storage sites. The biological half-life is about 50 days. Cholecalciferol has a slow onset but long-lasting effect. Plasma half life is 19-25 hours.

Biotransformation:
Vitamin D is metabolized in the kidney and liver.
Cholecalciferol is converted to the 25-hydroxycholecalciferol (25 (OH) D3, calcidiol) derivative which is a primary storage form of vitamin D3 by the mitochondrial 25-hydroxylase enzyme in the liver. This metabolite is further hydroxylated in the kidneys by vitamin D 1-α hydroxylase enzyme and converted to the active metabolite form 1,25- hydroxycholecalciferol ($1,25(OH)_2D_3$, calcitriol). 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. Metabolites are involved in the circulation by binding to specific alpha globulin.

Elimination:
Vitamin D compounds and its metabolites are mainly excreted through bile and feces. Little amounts are eliminated through the urine. The major metabolite eliminated through the urine is calcitroic acid.
The maximum serum concentration of the primary storage form is reached approximately 7 days after administration of single dose oral cholecalciferol. Then 25 (OH) D3 is slowly eliminated with a serum half-life of about 50 days.
After high doses of cholecalciferol, the serum concentration of 25 (OH) D3 may increase for several months. Hypercalcemia due to overdose may last for weeks (see Section 4.9 Overdose and treatment).

Linearity/Non-linearity:
Pharmacokinetics is linear. Plasma levels increase with doses given.

**5.3. Preclinical safety data**
Overdose of vitamin D3 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**
*Tablet:*
Microcrystalline cellulose
Calcium phosphate dibasic, anhydrous (E341)
Lactose monohydrate (derived from cow milk)
Povidone
Crospovidone
Croscarmellose sodium
Colloidal silicon dioxide
Magnesium stearate

*Coating material (SheffCoat Brillant Silver 30712206):*
Hydroxypropylmethyl cellulose
Hypromellose type 2910
Triacetin
Glycerol triacetate
Talc
Mica based pearlescent pigment (titanium dioxide / mica)

**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 away from light.

**6.5 Nature and contents of container**
DESIFEROL is available in PVC / PVDC / Aluminum foil blister packs in boxes containing 40 and 60 film-coated tablets.

**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)**
2017/570

**9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION**
Date of first authorization: 09.08.2017
Date of latest renewal:

**10. DATE OF REVISION OF THE TEXT**
27.07.2022