SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Detremin, 2000 IU soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains cholecalciferol (vitamin D3) 2000 IU (equivalent to 50 microgram vitamin D3).

Excipient(s) with known effect:
Each capsule contains 8 mg of sorbitol (E420).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

The soft capsule is clear, slightly yellow, in oval shape. Capsule dimensions are 12 mm x 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of vitamin D deficiency, in adults and adolescents (children ≥12 years).
- Prophylaxis and treatment of vitamin D deficiency in malabsorption

4.2 Posology and method of administration

Posology

Recommended dose

Recommended dose for vitamin D deficiency:

Vitamin D status	**25(OH)D nmol/L***	**Daily dose**
Deficiency	<25	**1-2 capsules** 2000-4 000 IU

*Serum 25-hydroxycholecalciferol

The dose should be adjusted dependent upon serum levels of 25-hydroxycholecalciferol, the severity of the disease, and the patient´s response to treatment. Measurement of 25(OH)D, serum phosphate, and serum calcium is recommended 1-3 months after treatment initiation. When relevant,

measurements should also include serum albumin, serum ALP (alkaline phosphatase), and serum creatinine.

A regular daily dose of 2000 IU (one capsule) raises serum 25-hydroxycholecalciferol (25(OH)D) in average by approximately 50 nmol/l within 4-5 months in adults.

The dose in adults and adolescents should not exceed 4000 IU (2 capsules) per day.

After initial correction of the vitamin D deficit for 3 - 6 months, the dose should be adjusted to a lower maintenance dose. The dose, treatment duration and the necessity of further monitoring shall be individualized, guided by the diagnosis, the severity of the disease and the patient's response to treatment.

Treatment of vitamin D deficiency in malabsorption:
1 capsule per day. The dose may be adjusted up to 5 capsules per day under monitoring.

Prophylaxis of vitamin D deficiency in malabsorption:
1 capsule per day

Special populations

Elderly population
No dose adjustment is required.

Renal impairment
Detremin should not be used in combination with calcium in patients with severe renal impairment. See section special warnings and precautions for use.

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.

Overweight patients
Patients with higher BMI may need higher doses to raise serum 25(OH)D to the desired level.

Hepatic impairment
No dose adjustment is needed.

Pediatric population
Detremin is not recommended in children below the age of 12 years.

Method of administration
Oral use. The capsule should be swallowed whole with water.

Detremin may be taken independently of meals (see section 5.2).

4.3 Contraindications

Detremin must not be used in:
-hypersensitivity to the active substance or to any of the excipients listed in section 6.1**.**
-hypercalcaemia
-hypervitaminosis D

Detremin must not be used in combination with calcium in patients with severe renal impairment.

4.4 Special warnings and precautions for use

If Detremin is given together with other vitamin D 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, see section 4.9. Intake of large doses of vitamin D (4000 IU/day or higher) for a long time may lead to a decrease in bone mineral density. Serum levels of 25-dihydroxyvitamin D above 125 nmol/L can potentially be harmful. The recommended dose should not be exceeded.

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 (for instance nephrocalcinosis) should be taken into account. If hypercalcemia or hypercalciuria is identified, the drug should be stopped. In patients with severe renal impairment, Detremin should not be used in combination with calcium.

At high doses of vitamin D_3, the serum calcium levels and urinary calcium should be monitored. Particular caution is recommended in patients with a history of renal calculi.

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 increased metabolism of vitamin D into its active form, in addition to patients with disorders associated with an increased risk of developing hypercalcemia (such as certain malignancies or thyrotoxicosis). These patients should be monitored with regard to the calcium content in serum and urine.

Treatment with cholecalciferol for a longer period of time should be monitored yearly with serum calcium, serum creatinine, and serum albumin. Surveillance is of particular importance in patients receiving cardiac glycosides, certain diuretics and lithium (see section 4.5). In elderly individuals hypervitaminosis D has been associated with an increased risk of falling. The recommended dose should not be exceeded.

Detremin is not recommended to children younger than 12 years.

4.5 Interaction with other medicinal products and other forms of interaction

- Phenytoin and barbiturates may diminish the effect of cholecalciferol by stimulating the conversion of 25-hydroxycholecalciferol and 1,25-dihydroxicholecalciferol to inactive calcitroic acid. Dose adjustments may be necessary.
- Rifampicin and isoniazid may reduce the effectiveness of cholecalciferol. Dose adjustments may be necessary.
- Patients treated with cardiac glycosides may be extra susceptible to high calcium levels and should have EEG parameters monitored.
- Simultaneous administration of benzothiadiazine derivatives (thiazide diuretics) increases the risk of hypercalcaemia due to decreased excretion of calcium in the urine.
- Treatment with cholecalciferol may increase the intestinal absorption of aluminium.
- If cholecalciferol is combined with metabolites or analogues of vitamin D careful monitoring of serum calcium levels is recommended.

- Glucocorticoids may increase the metabolism and elimination of vitamin D. Dose adjustments may be necessary.
- Treatment with lithium may increase the risk of developing hyperparathyroidism. Concomitant treatment with cholecalciferol should be carefully monitored with serum calcium.
- Laxative containing paraffin oil may inhibit the absorption of fat soluble vitamins
- Drugs that causes a reduction in fat absorption such as orlistat, or bile acid sequestrants such as cholestyramin, may decrease the absorption of vitamin D. Dose adjustments may be needed.

4.6 Fertility, pregnancy and lactation

A sufficient intake of vitamin D is necessary during pregnancy and lactation. The recommended intake of vitamin D follows the national and European guidelines and is considered to be approximately 600 IE.

Pregnancy
Detremin can be used during pregnancy, in case of a vitamin D deficiency. During pregnancy, the daily intake should not exceed 4000 IU of vitamin D. Doses above 600 IU should only be taken if strictly indicated and necessary to correct vitamin D deficiency. Prolonged overdose of vitamin D may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy.

Studies in animals have shown teratogenic effects of high doses of vitamin D (see section 5.3). There are no indications that vitamin D at therapeutic doses is teratogenic in humans.

Breast-feeding
Detremin can be used during breast-feeding. Vitamin D and its metabolites are excreted in human milk. This should be considered when giving additional vitamin D to the child.

Fertility
There are no data on the effect of high doses of vitamin D on fertility. However, 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
No studies on the effects on the ability to drive and use machines have been performed. Detremin has no known side effects which are likely to affect the ability to drive and use machines.

4.8 Undesirable effects
Frequencies of adverse reactions are unknown. The following reactions have been reported:

Gastrointestinal disorders:
Frequency unknown: constipation, flatulence, nausea, abdominal pain, diarrhoea.

Metabolism and nutrition disorders:
Frequency unknown: hypercalcaemia, hypercalciuria

Skin and subcutaneous tissue disorders:
Frequency unknown: hypersensitivity reactions such as pruritus, rash, urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 listed in Appendix V.

4.9 Overdose

Acute or chronic overdose of vitamin D can cause hypervitaminosis D and hypercalcaemia. Symptoms of hypercalcemia are tiredness, psychiatric symptoms (e.g., euphoria, dazedness, disturbed consciousness), nausea, vomiting, lack of appetite, weight loss, thirst, polyuria, formation of renal calculi, nephrocalcinosis, extraosseous calcification and kidney failure, changes in ECG, arrhythmias, and pancreatitis. In isolated cases the course has been described as fatal.

If a massive dose has been ingested ventricular emptying may be considered, together with administration of carbon. Sun light and further administration of vitamin D or calcium should be avoided. Rehydration and treatment with diuretics, e.g. furosemide 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 analogues, ATC code: A11CC05

In its biologically active form vitamin D_3 stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. 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.

5.2 Pharmacokinetic properties

Vitamin D_3 is metabolised into the active metabolites 25-hydroxycholecalciferol and 1,25--dihydroxycholecalciferol.

At alimentary doses vitamin D_3 is almost completely absorbed. Vitamin D_3 requires fat to be absorbed in the intestine. The fact that Detremin contains oil facilitates intestinal absorption, and therefore Detremin may be taken independently of meals. T max of the active metabolite 25-hydroxycholecalciferol is reached after about a week after a single dose.

Vitamin D_3 is stored in the fatty tissue and its biological half-life is approximately 42 days. Vitamin D_3 and its metabolites circulate in the blood bound to vitamin-D binding protein.

Vitamin D3 is metabolised to the active metabolite 25-hydroxycholecalciferol which is further metabolised to the active metabolite 1,25-dihydroxycholecalciferol.

25--hydroxycholecalciferol is slowly eliminated with an apparent half-life in serum of 42 days, due to the slow elimination of the parent compound. Elimination occurs mainly through the bile and faeces, but to some extent in urine.

Elimination occurs mainly through the bile, but to some extent in urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. Normal vitamin D levels is not potentially mutagenic (Ames test). No carcinogenicity studies

have been performed. There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Refined Olive Oil
DL- Alpha Tocopherol (Vitamin E)

Capsule shell
Gelatin
Glycerol
Water
Sorbitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

43 months.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass bottles sealed with aluminum seal and aluminum screw cap as a closure system. The glass bottle is packaged in a carton box.

Pack sizes: 90 or 250 soft capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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SE-114 51 Stockholm, Sweden
Tel: +46 18 7001140
e-mail: info@renapharma.se

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2024-11-08