SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Detremin 800 I.U./drop oral drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution (25 drops) contains 0.5 mg cholecalciferol, equivalent to 20,000 I.U. vitamin D_3.

1 drop contains 20 microgram cholecalciferol, equivalent to 800 I.U. vitamin D_3.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution.

Clear, weakly yellowish, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of:
- vitamin D deficiency or insufficiency
- secondary hyperparathyroidism

Prophylaxis and treatment of vitamin D deficiency in malabsorption.

Supportive treatment of osteoporosis in combination with calcium and a specific osteoporosis treatment

4.2 Posology and method of administration

Posology
In general, the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. Measurement of 25(OH)D and calcium is recommended 1 month after treatment initiation. 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.

The dose in adults and adolescents (age 11-17 years) should not exceed 4,000 I.U. (5 drops) per day, children (age 1-10 years) 2000 IU/day and infants (age 0-1 year) 1000 IU/day. For adult patients with malabsorption, the daily dose should not exceed 9600 IU.

A regular daily dose of 800 I.U. (one drop) raises serum 25(OH)D in average by approximately 20 nmol/l within 4-5 months in adults.

The dose can be administered as daily doses or be given once a week.

Vitamin D deficiency or insufficiency:

Vitamin D status	25(OH)D nmol/L*	Daily dose	Weekly dose
Deficiency	<25	**3-5 drops** 2,400-4,000 I.U.	**21-35 drops** 16,800-28,000 I.U.
Insufficiency	25-50	**1-2 drops** 800-1,600 I.U.	**7-14 drops** 5,600-11,200 I.U.

*Serum 25-hydroxycalciferol

Secondary hyperparathyroidism:
1-4 drops daily or 7-28 drops weekly.
In addition to measurements of serum 25(OH)D and calcium levels, measurements of PTH levels are recommended.

Prophylaxis and treatment of vitamin D deficiency in malabsorption:
Prophylaxis: 1-3 drops daily or 7-21 drops weekly.
Treatment: 3-12 drops daily or 21-84 drops weekly.

Osteoporosis in combination with calcium:
Supportive treatment along with specific osteoporosis treatment: 1 drop daily or 7 drops weekly.

Special populations

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.

Patients with malabsorption
Patients with malabsorption may require an upward dose adjustment

Hepatic impairment
No dose adjustment is needed.

Elderly population
No dose adjustments are required for elderly receiving doses lower than 4000 IU/day.

Paediatric population
Vitamin D deficiency and insufficiency:
Age < 1 year: 1 drop daily or 7 drops weekly.
Age 1-10 years: 1-2 drops daily or 7-14 drops weekly.
Age > 10 years: 1-5 drops daily or 7-35 drops weekly.

Secondary hyperparathyroidism:
Age < 1 year: 1 drop daily or 7 drops weekly.
Age 1-10 years: 1-2 drops daily or 7-14 drops weekly.
Age > 10 years: 1-5 drops daily or 7-35 drops weekly.

Prophylaxis and treatment of vitamin D deficiency in malabsorption:
For treatment of vitamin D deficiency due to malabsorption, the dose may be adapted to the degree of malabsorption and vitamin D-deficiency.

Age < 1 year: 1 drop daily or 7 drops weekly.
Age 1-10 years: 1-2 drops daily or 7-14 drops weekly.
Age > 10 years: 1-5 drops daily or 7-35 drops weekly

Maintenance dose: 1 drop daily or 7 drops weekly.
Calcium supplementation is advisable during the first weeks of therapy in the growing child.

The daily dose for adolescents (age 11-17) should not exceed 4000 I.U. (5 drops) per day, for children (age 1-10) 2000 I.U./day and for infants (age 0-1) 1000 I.U./day.

Method of administration
Oral use. Detremin may be taken independently of meals (see section 5.2).
The bottle should be slowly turned upside down to allow air to enter the bottle. It may take several seconds to achieve the first drop. The following drops will come slightly faster. The drops are preferably taken with a spoon. Care should be taken that the entire dose is ingested.

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.

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.

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.

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, 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 vitamin D_3 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.

4.5 Interaction with other medicinal products and other forms of interaction

- Phenytoin and barbiturates may diminish the effect of vitamin D_3 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 vitamin D_3. Dose adjustments may be necessary.
- Patients treated with cardiac glycosides may be extra susceptible to high calcium levels and should have ECG parameters and calcium levels monitored.
- Simultaneous administration of benzothiadiazine derivatives (thiazide diuretics) increases the risk of hypercalcaemia due to decreased excretion of calcium in the urine.
- Treatment with vitamin D_3 may increase the intestinal absorption of aluminium.
- If vitamin D_3 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 vitamin D_3 should be carefully monitored with serum calcium.
- Laxatives 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

Pregnancy
Detremin can be used during pregnancy, in case of a vitamin D deficiency.

Studies in animals have shown reproductive toxicity 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 Detremin 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:

Metabolism and nutrition disorders:
Frequency unknown: hypercalcaemia, hypercalciuria

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

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

Symptoms:

Acute or chronic overdose of vitamin D can cause 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 their course has been described as fatal.

Treatment:

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

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 thus facilitates intestinal absorption, and therefore Detremin may be taken independently of meals. Vitamin D_3 is stored in the fatty tissue and its biological half-life is approx. 50 days. After a single dose of vitamin D_3 maximum serum concentrations of the active metabolite 25-hydroxycholecalciferol are reached after about a week. 25-hydroxycholecalciferol is then slowly eliminated with an apparent half-life in serum of about 50 days, due to the slow elimination of the parent compound. 25-hydroxycholecalciferol is metabolised to the active metabolite 1,25-dihydroxycholecalciferol. After high vitamin D_3 doses serum 25-hydroxycholecalciferol concentrations can be increased for a month or two. Hypercalcaemia resulting from overdose can persist for several weeks.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. 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

Medium chain triglycerides.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Shelf life after first opening of container: 6 months.

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Dropper container with 3.6 ml solution (90 drops à 800 IU vitamin D_3) or 10 ml solution (250 drops à 800 IU vitamin D_3).

Container: 10 ml molded glass bottles, brown, glass type III.

Dropper: Dropper made of polyethylene, colourless.

Closure: Screw cap made of polypropylene, white.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Renapharma AB
Riddargatan 16,
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

2011-03-16/2016-03-16

10. DATE OF REVISION OF THE TEXT

2024-02-12