LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Detremin
(cholecalciferol)

This module reflects the scientific discussion for the approval of Detremin. The procedure was finalised on 2022-10-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Detremin, 800 IE, 2000 IE, 25 000 IE, Capsule, soft.

The active substance is cholecalciferol. A comprehensive description of the indication and posology is given in the SmPC.
For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, addition of a new pharmaceutical form, of the previously authorised product: Detremin, 800 IU, oral solution marketed by Renapharma AB since 2011.

The application for Detremin, 800 IU, 2000 IU, 25 000 IU, capsule, soft, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Renapharma AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member state (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
Cholecalciferol is absorbed up to 80 % in the small intestine by passive diffusion, which is facilitated by the presence of dietary fat. Furthermore, it is formed from 7- dehydrocholesterol in the skin by UV irradiation.

Cholecalciferol is metabolized in a two stage hydroxylation process. The first stage is hydroxylation to 25-hydroxycholecalciferol [25(OH) D3] in the liver. Calcitriol, (1alpha, 25-dihydroxycholecalciferol) is then formed in the kidneys by a second hydroxylation process. The synthesis of calcitriol in the kidneys is through a feed-back mechanism controlled by the concentrations of vitamin D, calcium and phosphate. Recent results indicate that several tissues besides the kidneys can synthesize vitamin D. The amount of tissue related calcitriol production is depending on the circulating 25-OH-vitamin-D3 level.

Pharmacokinetics
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Toxicology
Applicant has presented results from the public domain regarding oral LD50 studies for vitamin D in rat and dog as well as high dose levels administrated to dog for 10 days resulting in abnormal calcium deposits, rupture of elastic fibres and disorganization of collagen.

The mutagenic potency cholecalciferol was investigated by Ames test according to standard protocol in the presence and absence of a metabolic activating system. Cholecalciferol did not have any mutagenic effects in these tests.

Applicant states that carcinogenic studies in animals of cholecalciferol are not available in the literature.

Studies in pregnant rats and rabbits indicate a teratogenic risk. Applicant has not presented any studies on fertility and early foetal development, pre- and postnatal toxicity or studies in juvenile animals.

In conclusion, the non-clinical overview is very limited and none of the literature references are up to date. Many of the citations referred to are book chapters and thus not acceptable as literature references. However, due to the type of application, (extension of an already existing product, i.e. Detremin oral drops, an Art. 10a well-established use product), and the long clinical experience of the benefit-risk in the use of vitamin D supplementation, this can be acceptable.

Environmental Risk Assessment (ERA)
According to Guideline on the Environmental Risk Assessment of Medicinal use (EMEA/CHMP/SWP/4447/00) an Environmental Risk Assessment (ERA) is not required for vitamins because they are unlikely to result in significant risk to the environment.

Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, cholecalciferol is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
In a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. The product is intended to be a complement to dietary vitamin D3, which might be highly variable, and a potential minor difference in in vivo release properties from two different pharmaceutical forms would not be expected to lead to a different therapeutic profile. Further the dose is individualized and adjusted based on serum levels of cholecalciferol and patients' response. The intent of supplementation treatment is to increase the body deposit of D3 on a long-term basis. Moreover, as the absorption of vitamin D3 is controlled by a number of physiological processes and factors, the true absorption of these partly endogenous substances may be difficult to determine in a bioavailability study. The lack of BE-studies is acceptable and a sufficient bridge to literature data is considered established.

As this is a line extension, new pharmaceutical form, the pharmacokinetic assessment is focused on new data and SmPC claims not included in the SmPC of the already approved product Detremin, 800 IU, oral solution. In general the section of clinical pharmacology in the clinical overview is brief but sufficient for this Application.

Pharmacodynamics
Following summary is largely based on documents from European Food Safety Authority (EFSA) e.g. Scientific opinion on the tolerable upper intake level of vitamin D, EFSA Journal 2012;10(7):2813:

The principal function of the biologically active vitamin D metabolite 1,25(OH)2D is to maintain calcium and phosphorus homeostasis in the circulation, together with parathyroid hormone (PTH) and fibroblast growth factor (FGF-23).

If the serum ionised calcium concentration falls below a normal concentration of about 1.1–1.4 mmol/L, a cascade of events occurs to restore and maintain it within the range required for normal cellular and tissue functions.

The main target tissues of 1,25(OH)2D are the intestine, kidneys and the bone.

- In the intestine, 1,25(OH)2D binds to the vitamin D receptor (VDR) to facilitate calcium and phosphorus absorption by active transport.
- In the kidneys, 1,25(OH)2D stimulates the tubular reabsorption of calcium dependent on PTH that increases the production of 1,25(OH)2D from 25(OH)D in the proximal tubule. 1,25(OH)2D also downregulates the activity of the enzyme 1α-hydroxylase (CYP27B1), which is responsible for the conversion of 25(OH)D to 1,25(OH)2D in the kidney.
- In the bone, PTH and 1,25(OH)2D interact to activate the osteoclasts responsible for bone resorption. Osteoclasts then release hydrochloric acid and hydrolytic enzymes to dissolve the bone matrix and thereby release calcium and phosphorus into the circulation.

Clinical efficacy
Supplementation with 25(OH)D is to be considered as well established for the treatment of vitamin D

deficiency and insufficiency and as complement to a specific treatment of osteoporosis in combination with calcium. Since this application is a line extension, the applicant has not summarized the bibliographical efficacy data in the Clinical Overview. The Applicant has focused on the changes in the proposed dosages and the summary in the overview is based on primarily treatment guidelines. This is acceptable.

The indications proposed by the Applicant were in accordance with the indications for any of the vitamin D containing products presently on the market in the RMS. During the procedure the following indications were accepted:

The accepted indications for the soft capsule 800 IU are:

- Treatment of vitamin D deficiency or vitamin D insufficiency in adults and adolescents (children ≥12 years).
- Supportive treatment to a specific osteoporotic treatment together with calcium.

The accepted indications for the soft capsule 2000 IU are:

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

The accepted indications for the soft capsule 25,000 IU are:

- Treatment of vitamin D deficiency or vitamin D insufficiency in adults and adolescents (children ≥12 years)
- Supportive treatment to a specific osteoporotic treatment together with calcium.

The high dose capsule is intended to be administered once monthly. Monthly administration is currently not approved for the Detremin oral solution. The proposed doses for all indications, if calculated as daily doses are in the similar range as approved for Detremin solution. Monthly dosing can be acceptable based on studies showing that daily dosing versus monthly dosing with similar cumulative doses have similar effect on 25(OH)D3 serum levels.

Information on maintenance dose or length of the initial treatment period is included in all three products.

Recommendation that the dose should be adjusted dependent upon serum levels of 25-hyrdroxycholeclaciferol, the severity of the disease and the patient's response to treatment is included in the proposed SmPC in all three products.

Information on how much the proposed dose raises serum 25-hydroxycholecalciferol (25(OH)D) in average is included for the 800 and 2,000 IU capsules, but not for the 25,000 IU capsule. This is acceptable since it is recommended that the patient's serum levels should be measured.

Clinical safety

The following adverse events are mentioned in the SmPC for approved D-vitamin products: Hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea and hypersensitivity reactions such as pruritus, rash, urticaria.

Toxicity reported from vitamin D supplementation is rare. Toxicity manifests as hypercalcemia and hypercalciuria, leading to renal failure as a results of nephrocalcinosis and nephrolithiasis and neurologic symptoms including coma. Excessive vitamin D intake is associated with additional adverse events, including pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting and weight loss. These are all due to hypercalcaemia. The data on associations between vitamin D intake and increased risk for adverse long-term health outcomes is scarce and inconsistent.

The listed contraindications for the approved Detremin solution are

- 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
After a revision in the first round of the procedure the same contraindications are also listed for the soft capsules in the current application.

Overdose is the most common and most serious safety concern. Otherwise, the adverse event profile is benign.

The tolerable upper intake level (UL) of Vitamin D is 4000 IE daily in adolescents and adults (EFSA). The proposed dosing in the three products does not exceed the UL neither as daily dose nor when calculated from the proposed monthly doses. However, for the 2000 IU capsule and the indication treatment of vitamin D deficiency in malabsorption, the dose may be adjusted up to 5 capsules (10000 IU) per day under monitoring.

Except for the concerns regarding indications and posology as discussed in the section on efficacy, the safety of cholecalciferol in the dose proposed for the population targeted is considered to be sufficiently well documented by performed clinical studies and by long-standing clinical experience.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Detremin, oral solution, 800 IU/drop (20,000 IU/mL), Detremin, soft capsule, 800 IU, 2000 IU, and 25000 IU.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 9.1 is considered acceptable. A dated and signed version (9.2) was provided in response to a request in the D70 assessment.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The bridging was assessed and accepted at day 70.
The applicant has proposed a bridging to a user test carried out on the product Detremin 800 I.U./drop oral drops, solution.
The user test of the Detremin 800 I.U./drop oral drops, solution leaflet was assessed and accepted in SE/H/966/001/DC.
The proposed bridging regarding content and layout is considered acceptable.

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Detremin 800 I.U./drop oral drops, solution, SE/H/966/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The products in this application concern vitamin D3, cholecalciferol. Previously the MAH has provided a solution that were dosed as drops daily or weekly. The current Application concerns soft capsules with three different strengths; 800, 2000, and 25000 IU. The 800 IU and 25000 IU capsules have the same indications but differ in posology; the 800 IU capsule is for daily administration and the 25000 IU for monthly administration. The 2000 IU capsule has a slightly different indication to be administered as a daily dose.

The accepted indications for the soft capsule 800 IU are:

- Treatment of vitamin D deficiency or vitamin D insufficiency in adults and adolescents (children ≥12 years).
- Supportive treatment to a specific osteoporotic treatment together with calcium.

The accepted indications for the soft capsule 2000 IU are:

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

The accepted indications for the soft capsule 25,000 IU are:

- Treatment of vitamin D deficiency or vitamin D insufficiency in adults and adolescents (children ≥12 years)
- Supportive treatment to a specific osteoporotic treatment together with calcium.

The tolerable upper intake level (UL) of Vitamin D is 4000 IE daily in adolescents and adults (EFSA). The proposed dosing in the three products does not exceed the UL neither as daily dose nor when calculated from the proposed monthly doses. However, for the 2000 IU capsule and the indication treatment of vitamin D deficiency in malabsorption, the dose may be adjusted up to 5 capsules (10000 IU) per day under monitoring.

Recommendation that the dose should be adjusted dependent upon serum levels of 25-hyrdroxycholeclaciferol, the severity of the disease and the patient's response to treatment is included in the proposed SmPC section 4.2 in all three products. A proposal to include measurements of serum albumin, serum alkaline phosphatase, and serum creatinine is also provided.

The quality of the generic product, Detremin, is found adequate.

There are no objections to approval of Detremin, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Detremin, 800 IE, 2000 IE, 25 000 IE, Capsule, soft was positively finalised on 2022-10-05.

VIII. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary
SE/H/0966/002/II/023	Addition of a new indication for Detremin 800 IU: “Prophylaxis of vitamin D deficiency in adults and adolescents (children ≥12 years) with risk factors of vitamin D deficiency, see section 4.2.”	Yes	2026-04-24	-	The new indication for Detremin 800 IU and corresponding information in SmPC section 4.2 regarding risk factors of vitamin D deficiency relies on data based on the original medical authorisation application for Detremin and also clinical guidelines and recommendations foremost from the Swedish food agency.

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