LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Detremin
(cholecalciferol)

SE/H/966/01/DC

This module reflects the scientific discussion for the approval of Detremin. The procedure was finalised at 16 March 2011. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Renapharma AB has applied for a marketing authorisation for Detremin, oral drops, solution, 20 000 IU/ml. The active substance is cholecalciferol (vitamin D_3). For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Detremin is presented in the form of oral drops, solution, containing cholecalciferol 20 000 IU/ml, which corresponds to 0.500 mg/ml. The excipient is medium-chain triglycerides. The solution is filled in amber glass type III bottles with a polyethylene dropper.

II.2 Drug Substance

Cholecalciferol has a monograph in the Ph Eur.

Cholecalciferol is white or almost white crystals that are practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in trimethylpentane and in fatty oils. The structure of cholecalciferol has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Detremin, oral drops, solution, is formulated using excipients described in the current Ph Eur. The product does not contain any excipient of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as solubility and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the storage precaution “Keep the bottle in the outer carton, in order to protect from light”.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Vitamin D3 is a well-known substance with more than 10 years on the market. In this respect the applicant has presented sufficient nonclinical data on the main areas of toxicological investigations, i.e. conventional toxicity studies, genotoxicity and reproductive toxicity. No particular concerns are expected from the substitution therapy at recommended dosage, whereas overdosage is associated with severe adverse events from hypercalcaemia and teratogenicity in humans. Teratogenicity has also been noted in animal studies. The risk for teratogenicity from overdosage is sufficiently taken care of in the SPC.
The more product specific area of concern has been sufficiently addressed for Detremin and there is no particular concern regarding the impurity profile.

III.2 Ecotoxicity/environmental risk assessment

No ERA is needed for this substance.

III.3 Discussion on the non-clinical aspects

In conclusion, the applicant adequately presented a nonclinical evaluation of the product. Detremin can therefore be recommended for approval from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant has submitted a Clinical Overview and a Clinical Summary, authored by Mats Ehrnebo, (PhD, M. Pharm. Sci) and Mats Humble (MD). The Clinical Overview and the Clinical Summary are both of adequate quality. One hundred and twelve relevant literature references, dated 1991 – 2010, were submitted.

IV.2 Pharmacokinetics

No pharmacokinetic studies have been performed with the currently proposed oral drops product. There is, thus, no comparison with previously available products on the market regarding bioavailability of vitamin D from the formulation. As the formulation contains coconut oil and palm kernel oil, the applicant has discussed available literature data on the effect of different lipid content in the formulation on vitamin D absorption. It was suggested that the majority of human *in vivo* data indicate that the absorption of vitamin D is not influenced by the kind of formulation chosen: Fatty fish oil as compared to tablet formulation, olestra as compared to triglyceride placebo, whole milk as compared to skim milk or corn oil on toast, fatty cheese as compared to low fat cheese or liquid, both with or without food. On the other hand, some non-clinical and clinical studies demonstrated improved absorption from lipid-containing formulations. There are some data indicating that absorption may be optimised if vitamin D is taken with the major meal of the day, and that any differences between formulations with and without lipids are minimised if they are taken with a large meal. A recommendation to take this product with the major meal is therefore included in the SPC of Detremin. It cannot be excluded that malabsorption syndrome might affect absorption of vitamin D3 from an oily formulation. However, given that the SPC recommends monitoring of 25-hydroxyvitamin D levels, the dosage can be tailored in these patients and a decreased absorption can be overcome.

IV.3 Pharmacodynamics

Vitamin D is of fundamental importance for regulation of a number of essential physiological systems in the human body. The pharmacology and pharmacokinetics of cholecalciferol are well known. A clear dose response curve for vitamin D was seen in a number of different study populations. The dose needed to maintain acceptable serum levels of vitamin D seems to be greater than currently recommended daily intake, at least during winter time.
National and EU recommended daily intake of vitamin D is lower than recommended by several authors in modern literature.

IV.4 Clinical efficacy

It is in some aspects difficult to interpret the results from different studies on the daily need of vitamin D. The vitamin D doses resulting from sun exposure are manyfold higher than those supplied from food or from low dose vitamin D products. The amount of vitamin D intake from food varies widely between populations as well as between individuals. There are uncertainties around what harm low vitamin D levels do, and at what vitamin D level supplementation should be recommended.

Patients with malabsorption, regardless of underlying cause, need substitution of vitamin D, based on an individual assessment of the need.

Osteomalacia is usually caused by vitamin D deficiency, causing hypocalcemia. Osteomalacia can be caused by impaired intestinal uptake of vitamin D, by dietary insufficiency of vitamin D or by lack of sunlight exposure. Elderly persons, persons wearing clothes covering body and face, patients with lack of phosphate, with genetic aberrations or with chronic acidosis are prone to suffer from osteomalacia. Patients suffering from osteomalacia caused by vitamin D deficiency need vitamin D supplement.

Supportive treatment with calcium and vitamin D in a wide variety of doses and combinations has been used as additive treatment in most clinical trials in osteoporosis. This is a widely accepted indication for vitamin D. There has earlier been no consensus in support of the indication prophylaxis of osteoporotic fractures but recent review articles supporting this indication have been published.

Vitamin D3, in a number of different dosing regimens, could decrease PTH levels in patients with chronic kidney disease, in elderly and in postmenopausal patients.

The indications originally proposed by the applicant were not in accordance with the indication for any of the vitamin D containing products presently on the market in the RMS and were not exactly identical with (but similar to) those of the German originator. The present formulation was not considered appropriate for prophylaxis in children as the strength of the solution and the high total amount of vitamin D provided per container was considered inappropriate for small children, due to safety concerns. The applicant was asked to submit a revised proposal for indication and for dosage, adhering to the daily recommended intake for individuals without vitamin D deficiency, as recommended by the Swedish National Food Administration after thorough investigation. Recommendations should also be in accordance with directions from the Danish authority. The optimal dose of the product in treatment of vitamin D deficiency should be individually decided by the treating physician. Recommendations for monitoring schedules, for finding a suitable dose of vitamin D_3 for the individual patient, are now provided in the SPC, section 4.2.

After discussion, assessment of additional documentation submitted by the applicant, and revision of the SPC and PL, the following indications have been considered acceptable:

- Treatment of vitamin D deficiency or insufficiency (for definition, see section 4.2)
- Prophylaxis and treatment of Vitamin D deficiency in malabsorption
- Treatment of rickets in infants and children
- Treatment of osteomalacia caused by vitamin D deficiency
- Supportive treatment in osteoporosis, in combination with calcium and, when indicated, with a specific antiosteoporotic agent
- Prophylaxis in patients at increased risk of osteoporotic fractures, e.g. elderly patients and patients in glucocorticoid treatment, in combination with calcium
- Treatment of secondary hyperparathyroidism

IV.5 Clinical safety

Cholecalciferol as Vigantol oil® and Vigantoletten® 500 and 1000 is presently authorised world-wide in 22 and marketed in 19 countries and was marketed until 2007 as Vigantol® 50 000 solution for parenteral injection. Even if there is a great uncertainty in the estimation of total exposure to the product, it has been widely used.

The following adverse events are mentioned in the SPC for Detremin: hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea, and hypersensitivity reactions such as pruritus, rash, urticaria.
Serious adverse events recorded in PSURs were few and were in general related to overdose.

IV.6 Risk Management Plan

Due to the high concentration of cholecalciferol and the fact that there are other products on the market with significantly lower concentration and similar presentation, the Applicant was requested to provide a Risk Management Plan (RMP) which focused on the risk for over dosage and potential for medication errors (e.g. enhancement of product recognition and reduction of the possibility of a product mix-up). The RMP submitted was in line with the request of the RMS.

In order to reduce the risk for overdose the Applicant will perform routine pharmacovigilance activities in accordance with the pharmacovigilance plan. The Applicant has been requested to specifically address the risk for over dosage in coming Periodic Safety Update Reports (PSURs).

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

Overall conclusion

During this procedure the suggested indications for the product were amended, with proper justifications, the posology for the product was amended, and an approvable Risk Management Plan was presented.
The risk/benefit ratio was thereafter considered positive and Detremin, 20 000 IU/ml, oral drops, solution, was recommended for approval.

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Vigantol Oil. The Vigantol Oil leaflet was assessed and accepted in a type II variation (31191741/08), on 16/Mar/2009 (ref.no: 22194/55/08) by the Hungarian Health Authorities.
The bridging report submitted by the applicant has been found acceptable.

VI. APPROVAL

The Decentralised procedure for Detremin, 20 000 IU/ml, oral drops, solution, was successfully finalised on 16 March 2011.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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