COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol 25000 IU Focus Care, soft capsules

(cholecalciferol)

NL/H/4893/001/DC

Date: 21 October 2020

This module reflects the scientific discussion for the approval of Cholecalciferol 25000 IU Focus Care, soft capsules. The procedure was finalised at 21 June 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol 25000 IU Focus Care, soft capsules, from Focus Care Pharmaceuticals B.V.

The product is indicated for the initial treatment of clinically relevant vitamin D deficiency (serum 25(OH)D < 25 nmol/l) in adults.

A comprehensive description of the indications and posology is given in the SmPC.

Cholecalciferol has been widely marketed and used in the proposed indications for more than 10 years. Cholecalciferol is a well-established active substance in a variety of different pharmaceutical presentations.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of cholecalciferol. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

The concerned member state (CMS) involved in this procedure was Spain.

II. QUALITY ASPECTS

II.1 Introduction

Cholecalciferol Focus Care is red transparent, oval shaped soft gelatin capsule containing clear and colourless liquid. The capsules contain 0.625 mg vitamin D3 (equivalent to 25.000 IU cholecalciferol).

The hard capsules are packed PVC/PVDC/Aluminium foil blister packs.

The excipients are: all-rac-α-Tocopheryl acetate (E307), medium chain triglycerides, glycerol, gelatin (E441), sorbitol (E420) and ponceau 4R (E124).

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Cholecalciferol is a white to almost white, practically odourless crystalline powder. It is practically insoluble in water, freely soluble in ethanol (96

per cent) and soluble in trimethylpentane and in fatty oils. Issues in regard to polymorphism are not relevant, as the finished product is present in solution in the final finished product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the CEP and monograph in the Ph.Eur. with additional requirements for residual solvents. In addition, the microbiological quality of the active substance is controlled in accordance with Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Development trials of the capsules have been carried out with different combinations of excipients to finalise the manufacturing process and specifications. The use of the antioxidant is adequately justified. The development and the composition of the capsule shell has been described in sufficient detail. As the active substance is already dissolved and practically insoluble in water, dissolution testing is not deemed necessary. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of dissolving, heating, mixing, encapsulation, drying, inspection, polishing and packing. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients

Reference to Ph. Eur. is sufficient for Ph. Eur. excipients. For Sorbitol, liquid, partially dehydrated, the content of d-sorbitol and the content of 1,4-sorbitan has been stated. For colour ponceau 4R, in-house specifications are presented. These specifications are deemed acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification (cholecalciferol), identification tests for the anti-oxidant and colourants, average net content, individual net content, disintegration, uniformity of dosage units, assay, purity (any individual impurity and total impurities), loss on drying, and microbiological contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60%RH (12 months), 30°C/75%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to ICH stability guideline. On basis of the data submitted, a shelf life was granted of 24 months. The product should be stored in the original packaging in order to protect from light. The available stability data supports that there is no need to adopt a specific storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The gelatin is derived from animal source. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol Focus Care has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Cholecalciferol has been widely marketed and used in the proposed indications for more than 10 years. Cholecalciferol is a well-established active substance in a variety of different pharmaceutical presentations.

Vitamin D3 (cholecalciferol) is biologically inactive and requires metabolism, mainly within in the liver and kidney, to be converted to the hormonal form 1,25 dihydroxy-cholecalciferol (1,25(OH)2D). The most well-known effect of vitamin D is maintenance of normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. In addition vitamin D has widespread effects on cellular differentiation and proliferation, can modulate immune responsiveness and central nervous system function and may act as a chemo preventive agent against several malignancies including cancers of the prostate and colon.

The toxic action of vitamin D3 is usually attributed to a disturbance of whole-body calcium homeostasis. Significant lethality occurred in mice treated with a single high oral dose of calcitriol (4 mg/kg), the hormonal metabolite of cholecalciferol. Vitamin D was tested negative for genotoxic potential in the Ames test and a micronucleus assay. It is an endogenous substance produced naturally by contact of the skin by UV; therefore any cancer potential risk from this replacement therapy is not expected to exceed that of a population with normal vitamin D level. Overdoses of vitamin D should be avoided during pregnancy as permanent hypercalcemia has been related to adverse effects on the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans. The excipient profile and impurities observed are within the acceptable limit. Thus, overall no major toxicological findings of clinical relevance have been demonstrated in acute, subacute and chronic toxicity studies employing doses that are multiple times higher than the maximum recommended daily dose in humans.

III.2 Ecotoxicity/environmental risk assessment (ERA)

For vitamins, due to their nature, are unlikely to result in a significant risk to the environment. Also, it is expected that the product will substitute parts of the existing use and prescriptions of the currently marketed vitamin D products. No changes in a potential environmental risk that are not already known for vitamin D are to be anticipated.

III.3 Discussion on the non-clinical aspects

The application for Cholecalciferol Focus Care is based on well-established use. This is endorsed, since cholecalciferol has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and

toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacodynamics

The MAH has provided an extensive overview of general pharmacodynamic properties of vitamin D. Section 4.5 of the SmPC reflects the interactions of vitamin D with other medicinal products. The pharmacodynamic section is considered sufficiently described. Dosing is further discussed below in the clinical efficacy section.

IV.3 Clinical efficacy

The MAH has presented literature data of studies using different vitamin D doses. The proposed indication is acceptable in adults and in line with registered SmPC of comparable products.

Treatment of vitamin D deficiency in adults
The MAH submitted 19 studies (see literature list at the end of this report) to support the proposed indication and posology for treatment of vitamin D deficiency. These studies used a variety of dosing schedules to achieve normal 25(OH)D levels after a certain period of treatment including loading doses and/or several weeks or months of treatment.
For the initial treatment of clinically relevant vitamin D deficiency appropriate doses to be considered are in the range of 800-4000 IU/day as also indicated for instance in NL SmPCs of the Benferol (NL/H/3500/001-004) and Will Pharma (NL/H/2963/001-006) products. The proposed cumulative dose of 100000 IU (4 x 25000 IU) is therefore acceptable for the initial treatment of clinically relevant vitamin D deficiency. A lower maintenance dose should be considered one month after loading dose.

IV.4 Clinical safety

The safety profile of cholecalciferol is well-known. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia and hypercalciuria are the main adverse events.
Monthly vitamin D doses in adults are approved in some registered EU procedures. However, any specific discussion on the safety in high monthly dose is limited. Safety of monthly dose regimens in adolescents has not sufficiently been addressed. Of note, monthly doses of vitamin D in adolescents are currently not registered in the Netherlands.

The precautions of use in other special populations are sufficiently addressed in the SmPC. The SmPC as proposed is considered acceptable.

IV.5 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 that Cholecalciferol Focus Care.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Cholecalciferol Focus Care is considered widely established. For this authorisation, reference is made to clinical studies and experience with cholecalciferol. Cholecalciferol has been shown to be effective for the initial treatment of clinically relevant vitamin D deficiency in adults. The provided clinical overview is sufficient. No new clinical studies were conducted.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol 25000 IU Focus Care, soft capsules has a proven chemical-pharmaceutical quality. Cholecalciferol Focus Care is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well established use has been demonstrated for Cholecalciferol Focus Care, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 June 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

LITERATURE LIST

Bela E Toth, Istvan Takacs, Laszlo Szekeres, Boglarka Szabo, Bence Bakos and Peter Lakatos. Safety and Efficacy of Weekly 30,000 IU Vitamin D Supplementation as a Slower Loading Dose Administration Compared to a Daily Maintenance Schedule in Deficient Patients: A Randomized, Controlled Clinical Trial. J Pharmacovigil 2017, 5:4

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