COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol Pharmemma 1000 IU, 20000 IU and 50000 IU soft capsules

(cholecalciferol)

NL/H/5338/001-003/MR

Date: 15 July 2021

This module reflects the scientific discussion for the approval of Cholecalciferol Pharmemma 1000 IU, 20000 IU and 50000 IU soft capsules. The procedure was finalised at 4 March 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
RCT	Randomised Control Trial
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VDR	Vitamin D Receptor

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member State has granted a marketing authorisation for Cholecalciferol Pharmemma 1000 IU, 20000 IU and 50000 IU soft capsules from Pharmemma Limited.

The 1,000 IU strength is indicated for:

- Treatment of Vitamin D deficiency (serum 25(OH)D < 25 nmol/l) in adults, the elderly and adolescents.
- Prevention of vitamin D deficiency in high-risk patients in adults and the elderly.
- As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

The 20,000 IU and 50,000 strengths are indicated for use in adults and the elderly for:

- Treatment of Vitamin D deficiency (serum 25(OH)D < 25 nmol/l)
- Prevention of vitamin D deficiency in high-risk patients
- As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of soft capsules containing the active substance vitamin D3. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate 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. "Medicinal use" does not exclusively mean "use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The use of vitamin D supplementation as a treatment of vitamin D deficiency is supported by more than 10 years of clinical experience. Clinical trials have shown cholecalciferol to be an effective and well-tolerated treatment for both the treatment and prevention of these conditions. It was shown to be more effective than placebo. Oral formulations of cholecalciferol are widely available in the marketplace. Licenced cholecalciferol products include capsule presentations (40,000 IU, 20,000 IU/ 800 IU), oral drops (50,000 IU; 25,00 IU

2.5/ml; 10,000 IU/ml; 20,000 IU/ml/ 25,000 IU/2.5ml) and tablets (700 IU; 1000 IU; 30,000 IU).

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

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Cholecalciferol Pharmemma is a soft capsule:

- 1,000 IU: Green coloured clear transparent round shaped gelatin capsule with a clear, colourless liquid fill. Each capsule contains 25 micrograms cholecalciferol (vitamin D3), equivalent to 1,000 IU.
- 20,000 IU: Light-yellow coloured clear transparent round shaped gelatin capsule with a clear, colourless liquid fill. Each capsule contains 500 micrograms Cholecalciferol (vitamin D3), equivalent to 20,000 IU.
- 50,000 IU: Yellow coloured clear transparent round shaped gelatin capsule with a clear, colourless liquid fill. Each capsule contains 1250 micrograms Cholecalciferol (vitamin D3), equivalent to 50,000 IU.

The soft capsules are packed in HDPE containers with polypropylene cap and/or white opaque PVC/PVdC-Al blisters.

The excipients are:
Capsule content - medium chain triglycerides, vitamin E acetate (α-tocopheryl acetate) (E307)
Capsule shell - gelatin (E441), glycerol (E422), sorbitol liquid partially dehydrated, brilliant blue (E133) (only the 1,000 IU strength), quinoline yellow (E104) (only the 1,000 IU and 50,000 IU strengths) and purified water

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystal. Cholecalciferol is practically insoluble in water, freely soluble in ethanol (96%), soluble in trimethyl pentane and in fatty oils.

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. 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. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of dispensing, gelatin mass preparation, fill liquid preparation, encapsulation, drying, polishing and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches of each strength in accordance with the relevant European guidelines.

Control of excipients
Except for the non-compendial colourant agents, the excipients comply and are controlled in accordance with their respective Ph.Eur. monographs. The different colourants are controlled according to in-house specifications and are in compliance with Regulation 213/2012. The specifications are 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 of cholecalciferol and vitamin E, average weight of filled capsules, average net content, disintegration time, uniformity of mass, uniformity of content, uniformity of dosage unit, chromatographic

purity, assay, and microbial limits. 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 from three full-scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies are available covering 36 months storage at 25°C/60% RH and at 30°C/65% RH and six months at 40°C/75% RH. On basis of the data submitted, a shelf life was granted of 24 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
Stability data have been provided demonstrating that the product remains stable for 105 days following first opening of the container, when stored 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only material of animal origin included in the drug product. A TSE/BSE statement from the manufacturer has been provided, and on the CEP origin of the gelatin is described.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol Pharmemma 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

Cholecalciferol, also known as vitamin D3, can be synthesised in the skin from 7-dehydrocholesterol upon exposure to ultraviolet B radiation or it can be ingested as part of a normal diet in small quantities or taken as a supplement. It is biologically inactive and requires metabolism mainly within in the liver and kidney to be converted to the hormonal form 1,25 dihydroxycholecalciferol (1,25(OH)2D). 1,25(OH)2D binds to a nuclear receptor resulting in the transcription of a wide variety of genes. 1,25(OH)2D is a crucial mediator in calcium and phosphorous homeostasis and as such in bone metabolism. Studies have also found that cholecalciferol plays a role in a number of different areas. Vitamin D plays a role in calcium homeostasis and bone maintenance. In addition, vitamin D has extra-skeletal activities for instance on the immune system, in disease prevention like cancer, granulomatoses and kidney injury, on the cardiovascular system, skeletal muscles, on reproductive capacity on insulin sensitivity and glucose metabolism.

Safety pharmacology
With regard to safety pharmacology, neurological, cardiovascular, pulmonary or gastrointestinal effects nor abuse liability were noted upon intake of cholecalciferol.
In patients with impairment of renal function, cautiousness with administration of cholecalciferol is required and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and other forms of vitamin D should be used.

The pharmacodynamic properties of the active substance are well known and are adequately described in the nonclinical overview.

III.2 Pharmacokinetics

As cholecalciferol is lipophilic it is stored within the liver and adipose tissue from which it is slowly released. As such, the plasma half-life of vitamin D is considerably lower than its total body half-life. The metabolism of cholecalciferol is largely mediated through cytochrome P450 enzyme systems which result in increasingly polar metabolites, and ultimately lead to excretion through bile.

The pharmacokinetic properties of the active substances are well known and are adequately described in the non-clinical overview. The MAH has not provided additional studies. It is agreed that further non-clinical studies are not required. Pharmacokinetic drug interactions are adequately described in the SmPC.

III.3 Toxicology

The references reviewed regarding the acute and chronic toxic effects of cholecalciferol indicate a pattern of toxic effects related to hypercalcaemia, with calcification within soft tissue. The levels of exposure to cholecalciferol required to induce a toxic hypercalcaemia are dependent on the species of animal involved as well as on other factors, such as dietary calcium intake. Evidence is also available to show that the effects of chronic non-lethal toxicity can be reversible.
A study has shown that cholecalciferol is involved in the generation of proliferative lesions of the adrenal medulla of rats, including phaeochromocytoma (Tischler et al., 1999). However, evidence also exists that the anti-proliferative and apoptotic effects of cholecalciferol can provide some protection from carcinogenesis. There is no available data suggesting that cholecalciferol has any genotoxic effects.

Pre-cholecalciferol is biologically inert and must undergo a requisite isomerisation reaction to form cholecalciferol (Holick, 1994). Pre-cholecalciferol is believed to have a similar toxicity profile as cholecalciferol.

In order to discriminate between the different strengths, the following colouring agent are used; E104 Quinoline Yellow, E110 Orange Yellow S, Sunset Yellow FCF and E133 Brilliant Blue. E104 Quinoline Yellow was not genotoxic in an *in vitro* nucleus test with and without metabolic activation. No signs of carcinogenicity and reproduction or development toxicity were noted in long term studies in mice. In human, dietary exposure to Quinoline Yellow for children and all other age groups did not present a health concern (EFSA, 2015). E110 Orange Yellow S Sunset Yellow FCF was not genotoxic in *in vitro* and *in vivo* studies. No evidence of carcinogenic potential sunset yellow FCF was found. The temporary ADI of Sunset Yellow FCF is 1 mg/kg bw/day, which is higher than the maximum reported levels of use of Sunset Yellow FCF based on refined intake estimates. E133 Brilliant Blue is poorly absorbed and mainly excreted unchanged in faeces (EFSA, 2010). An ADI of 10 mg/kg bw/day was derived for Brilliant Blue FCF. For human, a theoretical maximum daily exposure of 8.1 mg/kg bw/day for adults, and 13.1 mg/kg bw/day for a typical 3-year-old child was determined by the EFSA in 2010.

The toxicological properties of the active substances are well known and are adequately described in the nonclinical overview.

III.4 Ecotoxicity/environmental risk assessment (ERA)

According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00) an ERA is not required for vitamins since they are unlikely to result in significant risk to the environment. The absence of an environmental risk assessment is thus considered acceptable.

III.5 Discussion on the non-clinical aspects

The application for Cholecalciferol Pharmemma soft capsules 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 Pharmacokinetics

Overall the pharmacokinetics are adequately summarised by the MAH, based on the available literature data. The (non-)clinical studies in published literature referred to, however, are on different product(s) than the product applied for. In accordance with part II of Annex I of Directive 2001/83, regarding article 10a applications, the MAH submitted bridging data to demonstrate that the product applied for is similar to the product(s) described in literature.

Absorption and distribution
Vitamin D can be obtained from the diet and by the action of sunlight on the skin. The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Only some selected food contains significant amounts of vitamin D2 and D3. Vitamin D is absorbed in the small intestine, a process that requires the presence of fat, bile (mainly deoxycholic acid) and pancreatic enzymes, and is transported via lymph incorporated in chylomicrons, to the liver.

Excretion
The metabolites of vitamin D analogues are excreted principally in bile and faeces. Although some vitamin D that is excreted in bile is reabsorbed in the small intestine, enterohepatic circulation does not appear to be an important mechanism for conservation of the vitamin. Following oral or intravenous administration of a single dose of radiolabelled calcitriol, 19–41% of radioactivity is recovered in urine within 6–10 days.

Metabolism
The metabolites of vitamin D analogues are excreted principally in bile and faeces. Although some vitamin D that is excreted in bile is reabsorbed in the small intestine, enterohepatic circulation does not appear to be an important mechanism for conservation of the vitamin. Following oral or intravenous administration of a single dose of radiolabelled calcitriol, 19–41% of radioactivity is recovered in urine within 6–10 days.

IV.3 Pharmacodynamics

Most biological effects of 1,25(OH)2D3 are mediated by binding of the ligand to its receptor, the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. The VDR was found originally in the classic vitamin D target organs involved in mineral homeostasis: the intestine, bone, kidney, and the parathyroid glands. More recently, the VDR has been detected in many other tissues and cells types as well. These non-classic vitamin D target organs respond to 1,25(OH)2D3 with a diverse range of biological actions including immunomodulation, the control of other hormonal systems, inhibition of cell growth, and induction of cell differentiation. The most critical role of 1,25(OH)2D3 in mineral homeostasis is to enhance the efficiency of the small intestine to absorb dietary calcium and phosphate.

Vitamin D induces bone mineralisation by increasing serum levels of calcium and phosphate. The higher potency of 1,25(OH)2D3 in regulating mineral homeostasis makes it the most likely vitamin D metabolite involved in bone mineralisation. 1,25(OH)2D3 also maintains normal serum calcium and phosphate by inducing bone resorption through enhancement of osteoclastogenesis and osteoclastic activity. Parathyroid hormone and 1,25(OH)2D3 directly affect calcium homeostasis, and each exerts important regulatory effects on the other. Whereas parathyroid hormone is the principal hormone involved in the minute-to-minute regulation of ionised calcium levels in the extracellular fluid, 1,25(OH)2D3 plays a key role in the day-to-day maintenance of calcium balance.

Secondary pharmacology comprises the effects of vitamin D extend beyond calcium homeostasis: the non-classical effects. The non-classic actions of vitamin D can be categorised into three general effects: regulation of hormone secretion, regulation of immune function, and regulation of cellular proliferation and differentiation. Because of these effects, ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60-70% of total mortality in high-income countries.

Multiple studies have been summarised by the MAH, regarding the association between vitamin D and diabetes/insulin secretion, the possible role in infections, autoimmune diseases like multiple sclerosis and inflammatory bowel disease, the possible role in cancer, and neuroprotective effects.

IV.4 Clinical efficacy

Vitamin D deficiency – prevention and treatment
Thirty-five studies focussing on treating vitamin D deficiency by supplementation of cholecalciferol were presented in the clinical overview. The observation period of studies is between 30 days to 4 year.

Vitamin D deficiency in osteoporosis and fractures
Several meta-analyses have addressed the issue of vitamin D supplementation and fracture. One meta-analysis of four randomised control trials (RCTs), each of which used a dose of 20 micrograms (800 IU) vitamin D daily, found that this dose prevents approximately 30% of hip or non-vertebral fractures compared with placebo in adults over the age of 65 years, and concluded that lower intakes are not effective (Vieth, 2005). Another meta-analysis, which included five RCTs for hip fracture and seven RCTs for non-vertebral fracture risk, concluded that oral vitamin D supplementation between 700 and 800 IU daily appears to reduce the risk of hip and any non-vertebral fractures in ambulatory or institutionalised elderly persons, but that an oral vitamin D dose of 400 units daily is not effective (Bischoff-Ferrari, 2005). An extension of this meta-analysis selected RCTs of oral vitamin D with or without calcium supplementation vs placebo/no treatment in post-menopausal women and/or older men (≥50 years) specifically reporting a risk of hip fracture. The pooled relative risk for vitamin D alone was 1.10 (95% confidence interval (CI), 0.89 to 1.36) and for vitamin D with calcium

was 0.82 (95% CI, 0.71 to 0.94). The authors concluded that these findings suggest that oral vitamin D appears to reduce the risk of hip fractures only when calcium supplementation is added (Boonen, 2007). A more recent meta-analysis of 12 RCTs added more weight to the earlier findings that higher doses of vitamin D (>400 IU daily) are needed to produce a significant reduction in risk of fracture (Biscoff-Ferrari, 2009).
Seventeen RCTs evaluated the effect of supplemental vitamin D2 or vitamin D3 on bone mineral density, predominantly in populations of late menopausal women.

Efficacy of cholecalciferol in vitamin D deficiency in pregnancy
Maternal vitamin D deficiency in pregnancy has been associated with an increased risk of pre-eclampsia, a condition associated with an increase in maternal and perinatal morbidity and mortality (Bodnar 2007; Holick 2008; Li 2002; Xiong 1999). In general, vitamin D 10 micrograms (400 units) a day is recommended for all pregnant women in accord with the national guidance.

The clinical benefit of treating and preventing vitamin D deficiency is well known, as well as the clinical benefit of adjunct to specific therapy for osteoporosis. The MAH provided an extensive overview of studies using a variety of dosing schedules of vitamin D to achieve normal 25(OH)D levels after a certain period of treatment. The bibliographic data submitted showed vitamin D deficiency was resolved or improved as indicated by increases in serum 25OHD levels.

IV.5 Clinical safety

Most of the safety database on cholecalciferol has been compiled from nutritional and post-marketing experience. Reference is made to what should be considered the higher daily intake level with some discrepancy between the literature (Hathcock 2007; Heaney, 2008; The European Food Safety Authority (EFSA) 2012).

The MAH further provided safety information based on information included in the several section of the SmPC.

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 loading doses in adults are approved in some registered EU procedures.

IV.6 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 Cholecalciferol Pharmemma.

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

Important identified risks	--
Important potential risks	--
Missing information	--

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

IV.7 Discussion on the clinical aspects

The use of cholecalciferol for the prevention and treatment of vitamin D deficiency and as an adjuvant therapy of osteoporosis is well established for more than 10 years, which is adequately shown in the overview given by the MAH. The safety profile of cholecalciferol is well-known. The indications and posology proposed for all strengths are in line with registered SmPC of comparable products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Vitamin D3 20,000 IU Capsules (IE/H/0443/01/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol Pharmemma 1000 IU, 20000 IU and 50000 IU soft capsules have a proven chemical-pharmaceutical quality. Cholecalciferol Pharmemma 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 state, on the basis of the data submitted, considers that well established use has been demonstrated for Cholecalciferol Pharmemma, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 4 March 2021.

VII. REFERENCES

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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