COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vitamine D3 Costero 5600 IU, 10000 IU and 25000 IU, tablets

(cholecalciferol concentrate)

NL/H/4990/001-003/DC

Date: 7 September 2023

This module reflects the scientific discussion for the approval of Vitamine D3 Costero 5600 IU, 10000 IU and 25000 IU, tablets. The procedure was finalised at 29 September 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 Vitamine D3 Costero 5600 IU, 10000 IU and 25000 IU, tablets, from Costero B.V.

The product is indicated in adults:

- for initial treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/l).
- prevention of vitamin D deficiency in adults with an identified risk.
- 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.

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 Luxembourg

II. QUALITY ASPECTS

II.1 Introduction

Vitamine D3 Costero is a white or almost white round or oval (25000 IU strength), biconvex tablet. The 5600 IU tablet has a scoring line on one side and is plain on the other side. The two higher strengths are plain on both sides. The tablets contain 0.14 mg (5600 IU), 0.25 mg (10000 IU) and 0.625 mg (25000 IU) cholecalciferol (vitamin D3).

The tablets are packed in transparent clear PVC/PVdC//Al blisters or polyethylene container closed with knurled on side polypropylene lid.

The excipients are: microcrystalline cellulose (E460), low-substituted hydroxypropyl cellulose (E463), anhydrous colloidal silica (E551), DL-alpha-Tocopherol (E307), modified food starch, medium chain triglycerides, sodium ascorbate crystalline (E301) and sucrose.

II.2 Drug Substance

The active substance is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Cholecalciferol concentrate (powder form) is a mix, namely Dry Vitamin D3 100 SD/S with cholecalciferol as active ingredient and excipients DL-alpha-Tocopherol, modified food starch, medium chain triglycerides, sodium ascorbate crystalline, sucrose and silicon dioxide, colloidal. Cholecalciferol concentrate is white or yellowish-white and consists of small particles.

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. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of drug substance

Stability data are presented for three batches. No significant changes were observed in any of the parameters measured. In view of the results of the stability tests, the proposed shelf-life of 24 months when stored in unopened containers and at a temperature below 15°C is acceptable.

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. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are blending of the ingredients and compression. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients used in the tablet core (that are not part of the dry vitamin D3 100 SD/S powder) are acceptable; these are widely used in the pharmaceutical industry and described in the Ph.Eur. 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 appearance, identification of the active substance, identification of the antioxidants, dimensions, average mass, uniformity of mass, hardness, assay, dissolution, disintegration, loss on drying, friability, uniformity of dosage units and microbiological purity. 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 for three pilot scaled batches for each strength 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 for each strength stored at 25°C/60%RH (9-24 months), 30°C/75%RH (9-12 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:

- Cholecalciferol 5600 IU tablets: 9 months when stored in opaque PVC/PVDC - ALU blister and 9 months when stored in plastic container pack
- Cholecalciferol 10000 IU tablets: 18 months when stored in opaque PVC/PVDC - ALU blister.
- Cholecalciferol 25000 IU tablets: 12 months when stored in opaque PVC/PVDC - ALU blister and 12 months when stored in plastic container pack

The proposed storage condition: “Store below 25°C. Store in the original package in order to protect from light” is acceptable,

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vitamine D3 Costero 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 is a secosteroid pro-hormone. It is converted to its active metabolite 25-hydroxycholecalciferol (25-OHD3) in the liver followed by its activation in kidney to 24,25-dihydroxyvitamin D3 [24,25-(OH)2D3] and 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3; calcitriol]. Calcitriol is a hormone, which performs biologic functions by regulating gene transcription through a nuclear high-affinity vitamin D receptor (VDR). This active metabolite of vitamin D binds to the nuclear VDR, which binds retinoic acid X receptor to form a heterodimeric complex that binds to specific nucleotide sequences in the DNA known as vitamin D response elements. Once bound, a variety of transcription factors attach to this complex, resulting in either up-regulation or down-regulation of the gene's activity.
In bones, vitamin D administration alleviates rickets and osteomalacia by stimulating the mineralisation of the organic matrix of bone. In intestine, vitamin D stimulates calcium (Ca) absorption against an electrochemical potential gradient. Vitamin D increases renal tubular reabsorption of Ca and retention of Ca by kidney. It decreases the level of PTH. 25-OHD3 at 100-200 nmol/L can induce the early and later osteoblast differentiation and bio-mineralisation. 1,25-(OH)2D3 stimulates bone resorption in vitro in concentrations normally used in cell cultures (10-10 M to 10-8 M). However, no nuclear receptors for 1,25-(OH)2D3 have been detected in osteoclasts. It corrects both the bone resorption and natural immune defects in the incisors absent osteopetrotic mutant.
In an ovariectomised (OVX) rat model, 25-(OH)2D3 promotes fracture healing by improving the histomorphometric parameters, mechanical strength and increases transformation of woven bone into lamellar bone. It suppresses osteoclastic hyperactivity and stimulates bone formation. Furthermore, 1,24-(R)-(OH)2D3, 1,25-(OH)2D3 and 1α-hydroxycholecalciferol [1α-OHD3] increase dose-dependently serum and urinary Ca, but decrease serum intact parathyroid hormone levels to the control level and prevent the development of osteoporosis histologically. In a closed tibial fracture model of rabbits, 1,25-(OH)2D3 exaggerated disuse osteoporosis and
prednisolone osteoporosis and impaired fracture healing. In dogs, the combination of Ca supplementation and cholecalciferol have shown systemic effects on accelerating bone regeneration. They stimulate bone remodelling. In glucocorticoid-induced osteopenia rats model, 1α-OHD3 acts on the gut, increasing Ca absorption (which was decreased by glucocorticoids), and 24,25-(OH)2D3 directly acts on bone to enhance bone formation and mineralisation. Chronic treatment with 1,25(OH)2D3 is effective to rescue the pseudo-vitamin D deficiency rickets phenotype of 1α-OHase mutant mice.

1,25-(OH)2D3 has shown anti-angiogenic activity in mouse oxygen-induced ischaemic retinopathy model. Cholecalciferol shows a potential therapeutic effect in normalising diabetes-induced alterations in cholinergic, insulin and VDR and maintains a normal glucose transport and utilisation in the cortex. It modulates muscarinic M3 receptors activity in pancreas and plays a pivotal role in controlling insulin secretion. 1,25-Cholecalciferol exerts an anticonvulsant effect independent of its role in Ca metabolism. Cholecalciferol, at doses of 1.0 and 2.5 mg/kg, has shown a profound anxiolytic-like effect in the experimental rat model of long-term oestrogen deficiency. Dietary cholecalciferol shows nticancer activity in mice.
In F1 New Zealand white mice, cholecalciferol at doses of 3 and 10 µg/kg i.v. may develop systemic lupus erythematosus. In rats and dogs, hypercalcaemia, hypercalciuria, hyperphosphatemia and ectopic calcification in the soft tissues can develop when exogenous 1,25-(OH)2D3 administered at doses of 22.5 µg/g orally (corresponds to ca 37.5 times of the recommended human dose [0.036 mg≈1428 IU/day] for 60 kg humans), on a mg/kg basis.
However, the chances of occur are negligible if used according to general clinical restrictions. Moreover, hypersensitivity reactions, hypercalcemia and hypercalciuria are stipulated in the MAH's SmPC.

III.2 Pharmacokinetics

In rats, cholecalciferol is absorbed in the small intestine and transported to the blood by the lymphatic system by a vitamin D-binding protein (a specific α-globulin). The absorption efficiency of cholecalciferol varies between 55% and 99% (mean 78%) in healthy subjects and between 66% and 75% in animals. In rats, 25-hydroxycholecalciferol (25-OHD3) is absorbed by a passive diffusion mechanism that is influenced by the intestinal pH, bile acid concentration, and thickness of the unstirred water layer. Approximately equal fractions of the infused hydroxylated vitamin are recovered from the lymphatic and biliary fluids. When the chylomicrons mix with plasma in vitro and in vivo, a significant fraction of cholecalciferol is transfer from the chylomicrons to vitamin D-binding protein. In rats, adipose tissue is the major storage site for cholecalciferol in its several forms, whereas liver and intestinal mucosa show the highest concentration of polar metabolites at 24 h. After absorption from the intestine, or synthesis in the skin, cholecalciferol is transported to the liver, where it is hydroxylated to 25-OHD3. This metabolite is then transferred to the kidney and converted to 24,25-dihydroxycholecalciferol [24,25-(OH)2D3] or 1,25-dihydroxycholecalciferol [1,25-(OH)2D3].
In the liver, this hydroxylation is mainly carried out by two enzymes in the rat, one found in the microsomes and the other in the mitochondria of hepatic cells. The metabolites of vitamin D analogues are excreted in bile and faeces in rats. In vitamin D-deficient male Wistar rats, animals dosed with radioactive 25-OHD3 show a higher radioactivity in their faeces, which may be explained by an increased biliary secretion due to the higher initial intestinal absorption.

In rats, concomitant use of cholecalciferol with prednisolone (glucocorticoid) decreases the effect of vitamin D, whereas with cholestyramine decreases absorption of cholecalciferol. In rabbits, anticonvulsant drugs (e.g., phenytoin and sodium valproate) inhibit bio-activation of

vitamin D, whereas, corticosteroids may diminish the effect of vitamin D in rats, when used concomitantly. These drug interactions are reflected in the MAH's SmPC.

III.3 Toxicology

Single-dose toxicity studies with cholecalciferol were conducted in mice, rats and dogs. The oral LD50 values of cholecalciferol were found in the range of 42.5 - 80 mg/kg, which correspond to ca. 1,012- 1,904 times the recommended human loading dose (2.5 mg ≈ 100,000 IU for 60 kg humans), on a mg/kg basis. Symptoms observed were anorexia, depression, muscle weakness, vomiting, polyuria, polydipsia, dehydration, abdominal pain, hematemesis, melena, and bradycardia.
Repeat-dose toxicity studies were conducted in rats (up to 26 weeks), and dogs (up to 26 weeks). In the 26-weeks toxicity study with cholecalciferol in rats, mild to moderate nephrocalcinosis was observed in all kidneys at 20,000 IU/kg which corresponds to ca. 840 times the recommended human dose (0.036 mg≈1,428 IU/day for 60 kg humans), on a mg/kg basis. However, medullary proliferative lesions (hyperplastic nodules and pheochromocytomas) were noted at 10,000 IU/kg which corresponds to ca. 420 times the recommended human dose, on a mg/kg basis. At 4 weeks the rats receiving 5,000 and 10,000 IU/kg (corresponds to 210- and 420-times the recommended human dose, on a mg/kg basis, respectively) of cholecalciferol showed extremely rare foci of kidney tubular calcification. Moreover, there is no evidence for an association between hypercalcaemia and pheochromocytomas in humans, suggesting an unusual susceptibility of rat adrenal medulla to perturbations of calcium homeostasis. In the 26-weeks dogs toxicity study with 1,25-dihyroxyvitamin D3, marked anorexia, severe weight loss, deterioration of physical condition, increased serum calcium and urea nitrogen, as well as other alterations in clinical laboratory measurements, calcification of soft tissue, bone resorption with replacement by fibrous tissue and irregular calcium deposits in the epiphyseal cartilage plates were observed at ≥0.08 µg/kg.
However, chance of occurrence in human is minimum if used according to general restrictions stipulated in the SmPC. Moreover, hypocalcaemia and hypercalciuria are reflected in the MAH SmPC.

Cholecalciferol and its derivatives 24,25-OHD3 and calcipotriol showed negative results in in vitro (Ames test [S. typhimurium strains TA98, 100, 1535, 1537 and E. coli strain WP2 uvrA], mammalian cell gene mutation test [mouse lymphoma L5178 TK assay], mammalian chromosome aberration test [Chinese hamster V79 cells]) as well as in vivo (bone marrow micronucleus assay and Comet assay) test systems. In a 26-week oral repeated dose study of cholecalciferol in male rats, pheochromocytomas, was observed in 1/10 animals at 0.25 mg/kg/day (corresponds to ca. 417 times the recommended human dose, on a mg/kg basis).
Moreover, pheochromocytomas is a rare tumour in humans with an annual frequency of 2 – 8 cases per million. The European Food Safety Authority (EFSA) Panel found no increased risk from exposure in the dose range 10 to 27.5 µg/day cholecalciferol for 4 to 7 years. Breast and colon cancer were the secondary outcomes in these trials. In addition, a reviewed meta-analysis of observational studies published up to 2011 found no association between 25-

hydroxycholecalciferol concentration and breast cancer (5 studies) or prostate cancer (11 studies). RAC considers that cholecalciferol should not be classified for carcinogenicity.

1,25-(OH)2D3 has no effect on fertility in rats. At high doses (100,000 IU [corresponds to ca. 4,202 times the recommended human dose, on mg/kg basis]) of vitamin D during pregnancy affect foetal death, maternal calcium and cholesterol homeostasis, neonatal calcium homeostasis and cause calcific aortic lesions in the mother and an apparent dose-related development of supravalvular aortic lesions in the new-born. Vitamin D has been reported to be teratogenic in animals at 4-15 times the recommended human dose. Offspring from pregnant rabbits treated with high doses of vitamin D had lesions anatomically similar to those of supravalvular aortic stenosis and offspring not showing such changes show vasculotoxicity similar to that of adults following acute vitamin D toxicity. The symptoms are most likely due to hypercalcaemia. These are stipulated in the MAH SmPC. Furthermore, it is reflected in the SmPC that during pregnancy woman should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.

Thus, preclinical data show that cholecalciferol has no special hazard for humans based on conventional studies if used according to general clinical restrictions.

III.4 Ecotoxicity/environmental risk assessment (ERA)

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.5 Discussion on the non-clinical aspects

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 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.

IV.3 Pharmacokinetics

The MAH provided an overview of pharmacokinetics data of Vitamin D available in literature. Vehicles such as oils, powders, and ethanol can be used in vitamin D supplements. The current application is for a tablet (powder) consisting of microcrystalline cellulose, low-substituted hydroxypropylcellulose, anhydrous colloidal silica, DL-alpha-tocopherol, modified food starch, medium chain triglycerides, sodium ascorbate crystalline and sucrose. The constituents of the to-be-marketed formulation are also used in other Vitamin D formulations on the Dutch market.
The MAH provided sufficient literature to conclude that different formulations of Vitamin D do not affect the PK of vitamin D. For example, Saadi et al. (2007) and Holvik et al. (2007) compared oil-based (oil supplement and fish oil) to powder-based vehicles (lactose tablet and micro-crystalline cellulose tablet) and indicated that oil and powder vehicles have similar bioavailabilities in normal subjects, since the differences did not reach statistical significance for either vehicle. Furthermore, Heaney et al. (2003) showed that lactose press-powder tablets and cellulose tablets did not lead to a significant difference in mean serum 25(OH)D increase. Therefore, it was sufficiently shown that the to-be-marketed product is similar to the products described in literature (needed for a well-established use application).

IV.4 Clinical efficacy

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

Treatment of vitamin D deficiency in adults
The proposed loading dose of once 10 Vitamine D3 Costero 10,000 IU tablets or 4 Vitamin D3 25,000 IU tablets (= 100,000 IU) is acceptable.

Prevention of vitamin D deficiency in adults
The proposed dose regimens of one or two Vitamine D3 Costero 5,600 IU tablets per week (equivalent to 800 IU or 1,600 IU/day, respectively), one Vitamine D3 Costero 10,000 IU tablet once a week (equivalent to 1,428 IU/day), or one Vitamine D3 Costero 25,000 IU every month (equivalent to 833 IU/day) is acceptable and in alignment with registered SmPCs.

Osteoporosis
The MAH proposed a dose of one or two Vitamine D3 Costero 5,600 IU tablets per week (equivalent to 800 IU or 1.600 IU/day, respectively), one Vitamine D3 Costero 10,000 IU once a week (equivalent to 1,428 IU/day), or one Vitamine D3 Costero 25,000 IU tablet every 3 weeks (equivalent to 1,190 IU/day). The proposed dose of one Vitamine D3 Costero 5,600 IU tablet per week is acceptable. A generally accepted dose of cholecalciferol for osteoporosis patients is 800-1,000 IU daily or its weekly or monthly equivalent. A daily dose of 2,000 IU vitamin D can be considered in frail elderly patients who are at particular risk of falls and fractures. A dose regimen of once per day, week, or month is acceptable.

IV.5 Clinical safety

The safety profile of cholecalciferol is based on data from various clinical studies published in literature (table 1)

Table 1. Studies on cholecalciferol and safety

Author	*Conclusions*
Soliman et al. 2010	Treatment with an intramuscular injection of 10 000 IU/kg vitamin D3 for 3 months in 40 rachitic children with vitamin D deficiency was safe and effective.
McCullough et al. 2017	Study of daily oral dosing with up to 60,000 IU of vitamin D3 for 2 to 6 years in 3 adult males. Concluding that prolonged daily dosing of vitamin D3 with doses of 10,000 to 60,000 IU was safe, no one developed hypercalcemia or any adverse events.
Grimnes et al. 2012	Descriptive study of serum 25(OH)D concentration and self-reported vitamin D intake in a community-based cohort (n=3,667, mean age 51.3±13.4 years). Serum 25(OH)D rose as a function of self-reported vitamin D supplement ingestion in a curvilinear fashion, with no intakes of 10,000 IU/d or lower producing 25(OH)D values above the lower-bound of the zone of potential toxicity (200 ng/ml). Unsupplemented all-source input was estimated at 3,300 IU/day. The supplemental dose ensuring that 97.5% of this population achieved a serum 25(OH)D of at least 40 ng/ml was 9,600 IU/day.
Nazarian et al. 2011	A small study showed that insulin sensitivity in vitamin D deficient subjects with impaired fasting glucose improved after 1-month treatment with cholecalciferol 10,000 IU/day. This result was independent of serum calcium, PTH, and BMI. It also demonstrated that use of high-dose cholecalciferol, 10,000 IU per day, was safe and not associated with hypercalcemia, nephrolithiasis, or other recognizable side effects.

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.
Safety of Vitamin D in the proposed dose regimen is sufficiently demonstrated. The precautions of use in other special populations are sufficiently addressed in the SmPC. The SmPC as proposed is considered acceptable.

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 that Vitamine D3 Costero.

Table 2. 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.7 Discussion on the clinical aspects

Vitamine D3 Costero is considered widely established. For this authorisation, reference is made to literature data and experience with cholecalciferol.

Benefits
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 bibliographic data submitted showed vitamin D deficiency was resolved or improved as indicated by increases in serum 25OHD levels. The applicant submitted and discussed several studies to support the treatment and prevention of vitamin D deficiency and osteoporosis.

Risks
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. Weekly and monthly vitamin D doses in adults are approved in some registered EU procedures.

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

Vitamine D3 Costero 5600 IU, 10000 IU and 25000 IU, tablets has a proven chemical-pharmaceutical quality. Vitamine D3 Costero 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 Vitamine D3 Costero, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 September 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
NL/H/4990/1-3/IA/001	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	No	22-03-2021	Approved	NA
NL/H/4990/1-3/IA/002	Change in the name and/or address of the marketing authorisation holder	Yes	06-03-2021	Approved	NA
NL/H/4990/1-3/IB/003	Extension of the shelf life of the finished product; As packaged for sale (supported by real time data)	Yes	06-03-2021	Approved	NA
NL/H/4990/IA/004/G	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	Yes	22-12-2021	Approved	NA
NL/H/4990/1-3-/IB/005	Change in the description or composition of the finished product; other variation	Yes	14-12-2021	Approved	NA
NL/H/4990/1-3-/IB/006	Change in the shelf-life or storage conditions of the finished product	Yes	18-02-2023	Approved	NA
NL/H/4990/1-3-/IA/007	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal	No	30-05-2023	Approved	NA

	products for human use				

LITERATURE LIST

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