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January 2017

Final Assessment Report

Mutual recognition Procedure

OVERVIEW

Cholecalciferol 1000/ 20.000/ 50.000 IU soft capsules (Cholecalciferol)

NL/H/5338/001-003/MR

Applicant: Pharmemma Limited, Ireland

Reference Member State	The Netherlands
End of Procedure	4 March 2021
Date of Final AR:	22 March 2021

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ADMINISTRATIVE INFORMATION

Name of the medicinal product in the RMS	Cholecalciferol Pharmemma
Name of the drug substance (INN name):	Cholecalciferol
Pharmaco-therapeutic group (ATC Code):	A11CC05
Pharmaceutical form(s) and strength(s):	Soft capsules; 1000/20.000/50.000 IU
Reference Number(s) for the Decentralised Procedure	NL/H/5338/001-003/MR
Reference Member State:	The Netherlands
Concerned Member States:	FR
Legal basis of application:	10a well-established use application
Applicant (name and address)	Pharmemma Limited Unit 2, Ashbourne Manufacturing Park Ashbourne Co. Meath A84 KH58 Ireland
Names and addresses of all proposed manufacturer(s) responsible for batch release in the EEA	[redacted]
Names and addresses of all proposed manufacturer(s) of the medicinal products	[redacted]
Names and addresses of all proposed manufacturers of the active substance	[redacted]

	[redacted]
Names and addresses of all proposed ASMF holders (if different from manufacturer of active substance)	*Not applicable*
Names and addresses of all proposed CEP holders (if different from manufacturer of active substance)	[redacted]
RMS contact person	[redacted]

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Cholecalciferol Pharmafile, in the treatment of Vitamin D deficiency, is approvable.

II EXECUTIVE SUMMARY

II.1 Problem statement

Pharmemma aims to obtain marketing authorization for Cholecalciferol 1000/ 20,000/ 50,000 IU Soft Capsules. Vitamin D is a well known substance used to treat vitamin D deficiency and osteoporosis, and the application is based on well established use (Directive 2001/83/EC article 10(a)).
The legal status of the products will be a Prescription Only Medicine (POM) for NL (for CMS FR 'not subject for medicinal prescription' is proposed for the 20.000 IU and 1000 IU strengths).

Vitamin D deficiency
Deficiency results in inadequate intestinal absorption of calcium and phosphate. Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%.
Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases.

II.2 About the product

Mode of action
About 80 % of orally ingested vitamin D is normally absorbed in the duodenum and jejunum. The first step, hydroxylation of vitamin D3 at the carbon-25 position resulting in formation of 25(OH)D3, occurs primarily in the liver and is catalysed by 25-hydroxylase. The second hydroxylation step occurs predominantly in the proximal tubule cells of the kidney and is carried out by 1-α-hydroxylase (CYP27B1), resulting in production of the biologically active metabolite 1, 25-dihydroxyvitamin D3 (1, 25(OH)2D3).

Pharmacological classification:
Pharmacotherapeutic group: Vitamin D and analogues, cholecalciferol
ATC code: A11CC05

Claimed indication and posology
The proposed indications are:
1000 IU strength
"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.

20,000/50,000 IU strengths:
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.

Indicated for use in adults and the elderly.

For the proposed posology please refer to the SmPCs.

II.3 General comments on the submitted dossier

With the Netherlands as reference member state in this decentralised procedure Pharmemma is applying for a marketing authorisation for Cholecalciferol 1000/ 20.000/ 50.000 IU Soft Capsules.

Legal basis: Well established use
The marketing authorisation application was submitted by Pharmemma in accordance with Article 10a of Directive 2001/83/EC as amended (well-established use (WEU) application). For a WEU application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. In a WEU application, results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Summary justification applicant
Vitamin D inadequacy constitutes a largely unrecognized epidemic in many populations worldwide. It has been reported in healthy children, young adults, especially African Americans, and middle-aged and elderly adults.
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 market place. Licenced cholecalciferol products include capsule presentations (40,000IU, 20,000IU/ 800IU), oral drops (50,000IU; 25,00IU 2.5/ml; 10,000IU/ml; 20,000IU/ml/ 25,000IU/2.5ml) and tablets (700IU; 1000IU; 30,000IU).

Bridging data
No bridging data has been submitted to bridge between the proposed drug products and the submitted literature.

PIP compliance
According to the 'paediatric regulation' (EC 1901/2006), a Paediatric Investigation Plan is not required for Article 10a applications.

RMP
A RMP has been submitted.

Scientific advice
No scientific advice was sought prior to this application.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GLP/GCP
Some of the literature provided and reviewed in this section is old and the experimental methods adopted may not always conform to Good Laboratory Practice (GLP) or current Good Clinical Practice (GCP). However, the literature provided and reviewed herein is sourced from peer reviewed journals, periodicals or standard medical texts and hence experiments performed and results reported are inferred to be obtained using standard methods and reliable for clinical and statistical evaluation. The tests methods for pharmacodynamics, pharmacokinetic, toxicological and clinical studies mentioned in literature conform to updated scientific knowledge comply with requirements and can be thoroughly followed.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
General information
The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia. The active substance is practically insoluble in water and is soluble in fatty oils. The drug substance appears as whit or almost white crystals. For cholecalciferol a CEP by [redacted] has been provided, i.e. CEP No. [redacted]

Manufacturing process
The manufacturing process of cholecalciferol is covered by the CEP.

Quality control of active substance
The active substance specification is in line with the Ph.Eur. monograph and additional requirements of the CEP.

Batch analytical data by the finished product manufacturer demonstrating compliance with the drug substance specification have been provided for drug substance batches supplied by [redacted]

Stability of drug substance
The retest period of the substance is 36 months if stored at [redacted] This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

Drug Product
Composition
The drug products are clear transparent round shaped soft capsules available in three different strengths, i.e. 1,000 IU, 20,000 IU and 50,000 IU cholecalciferol. Besides the active substance the capsule contents is composed of medium chain triglycerides and all-rac-alpha tocopherol acetate

(Vitamin E). The soft capsules are composed of gelatin, glycerol, partially dehydrated sorbitol liquid, purified water and colourants different for each strength. All three product strengths have the same capsule size and dimensions. All strengths except for the highest strength of 50,000 IU are packed in HDPE bottles with white opaque PP cap having wad with induction seal or in opaque PVC/PVdC-Al blisters. The highest product strength is only packed in blisters. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of comparator products and the optimization of the formulation. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

[redacted]

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

[redacted]

Stability of drug product

Stability data on the product has been provided on three production scaled batches per strength stored at 25°C/60% RH (36 months), 30°C/65% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC/PVdC-Al blisters and 23 ml HDPE bottles filled with 50 capsules (except for the 50,000 IU strength). [redacted]. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The claimed shelf-life of 24 months without any special storage conditions is justified.

In-use stability studies were performed for the batches packed in 50's count 23 ml HDPE bottles. The bottles were kept at 25°C/60% RH and opened for 5 minutes daily up to 105 days to simulate in-use conditions. [redacted]. The proposed in-use shelf-life of 105 days after opening of the bottles is considered justified.

Other information

Certificates of suitability issued by EDQM have been provided for the active substance and the excipient gelatin confirming compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products.

III.2 Non clinical aspects

Pharmacology
Colecalciferol, also known as Vitamin D3, can be synthesized 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 dihydroxycolecalciferol (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 colecalciferol 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 extraskeletal 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 Colecalciferol
In patients with impairment of renal function cautiousness with administration of colecalciferol 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 colecalciferol 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.

Pharmacokinetics
As colecalciferol 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 halflife. The metabolism of colecalciferol is largely mediated through cytochrome P450 enzyme systems which result in increasingly polar metabolites, and ultimately lead to excretion through bile.

For pharmacokinetic drug interactions is referred to the SmPC.

The pharmacokinetic properties of the active substances are well known and are adequately described in the nonclinical overview. The applicant has not provided additional studies. It is agreed that further studies are not required.

Toxicology
The references reviewed regarding the acute and chronic toxic effects of colecalciferol indicate a pattern of toxic effects related to hypercalcaemia, with calcification within soft tissue. The levels of exposure to colecalciferol 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 colecalciferol has an involvement 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 apoptic effects of colecalciferol can provide some protection from carcinogenesis. There is no available data suggesting that colecalciferol has any genotoxic effects.

Pre-colecalciferol is biologically inert and must undergo a requisite isomerisation reaction to form colecalciferol (Holick, 1994). Pre-colecalciferol is believed to have a similar toxicity profile as Colecalciferol. The finished product specification now states; Impurity A NMT 1.0 %, Any single impurity NMT 0.2% and Total Impurities NMT 2.0%

In order to discriminate between the different strengths, following colouring agent are utilized; E104 Quinoline Yellow 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 was noted in long term studies in mice. In human, detary exposure to Quinoline Yellow for children and all other age groups does not present a health concern (EFSA, 2015). 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.

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.3 Clinical aspects

No new clinical studies were conducted, since this concerns a bibliographical application.

Pharmacokinetics
The applicant did not perform clinical pharmacology studies and no biopharmaceutical clinical trials have been carried out. Overall the pharmacokinetics are adequately summarized by the applicant, 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 applicant 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 IV administration of a single dose of radiolabeled 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 IV administration of a single dose of radiolabeled calcitriol, 19–41% of radioactivity is recovered in urine within 6–10 days.

Pharmacodynamics
No new pharmacodynamic studies have been conducted and none are needed for this well-established use application. The Applicant has submitted literature up to 2017.
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 mineralization 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 mineralization. 1,25(OH)2D3 also maintains normal serum calcium and phosphate by inducing bone resorption through enhancement of osteoclastogenesis and osteoclastic activity. PTH (parathyroid hormone) and 1,25(OH)2D3 directly affect calcium homeostasis, and each exerts important regulatory effects on the other. Whereas PTH is the principal hormone involved in the minute-to-minute regulation of ionized 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 categorized 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% to 70% of total mortality in high-income countries.

Multiple studies have been summarized by the applicant, 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.

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 RCTs, each of which used a dose of 20 μg (800IU) 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 800IU 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 (>400IU 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 BMD, 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 (see the clinical report for relevant studies).

Conclusions clinical efficacy:
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 applicant 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.

The indications proposed for the 1000/20,000/50,000 IU are in line with registered SmPC of comparable products.
In general, the proposed posology is acceptable and in alignment with registered SmPCs and guidelines.

Clinical safety
Most of the safety database on colecalciferol 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 applicant further provided safety information based on information included in the section of the SmPC.

Adverse Effects of Cholecalciferol
Excessive intake of vitamin D leads to the development of hyperphosphatemia or hypercalcemia.
Other described adverse reactions are:
Metabolism and nutrition disorders:
Uncommon: Hypercalcaemia and hypercalciuria.
Gastrointestinal disorders:
Not known: Constipation, flatulence, nausea, abdominal pain, diarrhoea.
Skin and subcutaneous disorders:
Rare: Pruritus, rash and urticaria.

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

Summary Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's and Proposed Future MAH Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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

Safety specification
No safety concerns have been identified for Cholecalciferol Pharmascope. This is agreed.

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

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan (version 01, date of final sign off 7 20 November 2020) is considered acceptable.

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.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

Common renewal date
The common renewal date has been set 5 years after the date the NL national MA has been provided: 20 October 2025 (NL MA provided on 20 October 2020).

IV BENEFIT RISK ASSESSMENT

Benefits
The use of cholecalciferol for the prevention and treatment of vitamin D and as supportive treatment for osteoporosis is well established. Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%.
Large scale population studies show that low serum 25OHD is associated with a number of adverse outcomes in the human musculoskeletal, innate immune and cardiovascular systems. A causal relationship between vitamin D and musculoskeletal health has been well-established. Vitamin D in combination with calcium deficiency can cause rickets in children and osteomalacia in adults and may contribute, with other factors, to osteoporosis, falls and frailty in the elderly. In order to demonstrate the efficacy of vitamin D, the applicant has provided numerous publications.

Risks
The safety profile of cholecalciferol is well-known. In general, vitamin D is well tolerated. Hypercalcaemia and hypercalciuria are the main adverse events.

In general, the description of safety in the clinical overview is considered sufficient. Hypercalcaemia and hypercalciuria are the most common adverse events reported from clinical trials and post-

marketing data. Other adverse events less commonly reported affect the skin system leading to disorders such as pruritus, rash and urticaria.

Benefit-Risks Assessment
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 applicant.
The safety profile of calcium and cholecalciferol is well-known. Although uncommon, hypercalcaemia and hypercalciuria are the main adverse events

The indications and posology proposed for all strengths are in line with registered SmPC of comparable products.

V LIST OF QUESTIONS as proposed by RMS

V.1 Quality aspects

None

V.2 Non clinical aspects

None

V.3 Clinical aspects

None

VI RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

The capsules are subject to medical prescription in NL (for CMS FR 'not subject for medicinal prescription' is proposed for the 20.000 IU and 1000 IU strengths).

VI.2 Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

None

VI.3 Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC

None

VI.4 Product Information

The proposed Product Information is acceptable.

VI.5 Assessment of User Testing

The applicant submitted a bridging analysis to the Readability User Testing Report for Vitamin D3 20,000 IU Capsules (SEQ Ltd Report, Dated 20/10/2014, SEQ-RUT-2014–002 (parent PL). Assessment of the User Testing of the parent PL is attached in the 'QRD Guidance and Checklist for the Review of User Testing Results (Appendix VII). The applicant submitted the 'QRD form for submission and assessment of user testing bridging proposals'(Appendix VIII). Bridging regarding design/layout/format and content is acceptable.