COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol Acure 20.000 IU and 25.000 IU soft capsules (cholecalciferol)

NL/H/5450/001-002/DC

Date: 12 May 2023

This module reflects the scientific discussion for the approval of Cholecalciferol Acure 20.000 IU and 25.000 IU soft capsules. The procedure was finalised on 25 October 2022. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Acure 20.000 IU and 25.000 IU soft capsules, from Acure Pharmaceuticals Limited.

The product is indicated in adults for the initial treatment of clinically relevant vitamin D deficiency (serum levels < 25 nmol/L or < 10 ng/mL).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted via a decentralised procedure pursuant to Article 10a of Directive 2001/83/EC, which concerns a well-established use (WEU) application. Well-established medicinal use needs to be demonstrated for the active substance of the medicinal product for at least 10 years in the specific therapeutic area. In a WEU application, results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. Therefore, no clinical studies have been performed by the marked authorisation holder (MAH) and instead, bibliographical data are submitted.

Cholecalciferol as active substance in medicinal products have been in well-established medicinal use within the Community for more than ten years, with recognised efficacy and an acceptable level of safety. Bridging data has been submitted to bridge between the proposed drug products and the submitted literature.

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

II. QUALITY ASPECTS

II.1 Introduction

Cholecalciferol Acure 20.000 and 25.000 IU are soft capsules. The product strengths can be distinguished by the colour, size and shape of the capsules.

The 20.000 IU strength are transparent, blue, round with 7.2 mm of diameter, soft capsules with a seam in the middle, filled with light yellow viscous liquid. Each capsule contains as active substance 500 mg cholecalciferol (vitamin D_3), equivalent to 20.000 IU.

The 25.000 IU strength are white to almost white, oval with 12 mm of length and 6.7 mm of thickness, soft capsules with a seam in the middle, filled with light yellow viscous liquid. Each capsule contains as active substance 625 mg cholecalciferol (vitamin D_3) equivalent to 25.000 IU.

The excipients are:
Capsule fill - triglycerides, medium chain and all-rac-α-tocopheryl acetate (E307).

Capsule shell - gelatine (E441), glycerol (E422), purified water and patent blue V (E131) (only for the 20.000 IU strength) or titanium dioxide (E171) (only for the 25.000 IU strength).

The capsules are packed in Aluminium/Polyvinylchloride/Polyvinylidene chloride (Al/PVC/PVDC) blisters.

II.2 Drug Substance

The active substance is cholecalciferol (vitamin D_3), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance consist of white or almost white crystals and is practically insoluble in water, freely soluble in ethanol (96%), soluble in trimethylpentane and in fatty oils. No information on potential polymorphism has been reported in the literature. Physical characteristics of particle size and polymorphism have no impact on this formulation as the drug substance is present in solution in the 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. The specification is in line with the Ph. Eur. monograph and additional requirements of the CEP. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three drug substance batches from site I and four batches from site II.

Stability of drug substance

The active substance is stable for 36 or 60 months when stored under the stated conditions. The determined shelf-life depends on the storage temperature and used container. 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 development of the product has been described, the choice of excipients is justified and their functions explained.

The main development studies performed were the optimization of the formulation by using an antioxidant excipient and an overage of cholecalciferol and deciding the colour, size and shape of the capsules to facilitate differentiation of the strengths. The pharmaceutical development of the product has been adequately performed, the overage and the excipients used are justified.

Manufacturing process

The main steps of the manufacturing process are the preparation of the capsule fill solution, preparation of the gelatine mass, encapsulation, capsules drying, sorting and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches per strength.

Control of excipients

Except for the non-compendial colourant patent blue V (E131), the excipients comply and are controlled in accordance with their respective Ph.Eur. monographs. The colourant is controlled according to in-house specifications and it is 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 appearance, average filling mass, uniformity of dosage units by mass variation, identification of vitamin D_3, identification of the colourant patent blue V, disintegration time, assay of vitamin D_3 in a capsule, assay of α-tocopheryl acetate in a capsule, related substances and microbiological quality. Except for the vitamin D_3 assay and α-tocopheryl acetate, the release and shelf-life limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been submitted. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of three full scaled batches per strength, from the proposed production sites, have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches of each strength stored at 25°C/ 60% RH (long-term, 12 months), 30°C/75% RH (intermediate, 12 months) and 40°C/75% RH (accelerate, 6 months). The batches were stored in OPA/Al/PVC/Al blisters. Up-to-date results of long-term and intermediate studies are within the proposed limits without any significant variations or changes. In the accelerated study, significant change occurred at the final time point, when an unknown impurity exceeded relevant acceptance criteria. In addition, under the accelerated storage conditions, the capsules were observed to soften over time, melt and stick to the blister. The stability was tested in accordance with the ICH stability guidelines. Photostability studies as described in the ICH Q1B were performed and showed that the product is photosensitive. On basis of the data submitted, a shelf-life was granted of 27 months. The labelled storage conditions are *"do not store above 30°C. Store in the original package to protect from light and moisture".*

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for the active substance and for the excipient gelatine used in the empty capsule shell. 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 Acure 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

The MAH has provided a comprehensive and extensive overview of the primary and secondary pharmacodynamics of cholecalciferol. The primary pharmacodynamics included the mechanism of action of both, the genomic and nongenomic functions. Secondary pharmacodynamics included the widespread effects of vitamin D on the cellular differentiation and proliferation, immune responsiveness, regulation of hormone secretion and central nervous system (CNS) function. Furthermore, information regarding Vitamin D deficiency was included. Vitamin D deficiency is a worldwide problem because it is associated with an increased all-cause mortality. Special groups (infants, adolescents and the elderly) are at risks for vitamin D deficiency. Common causes of vitamin D deficiency include genetic defects in the vitamin D receptor, severe liver or kidney disease, and insufficient exposure to sunlight. Vitamin D deficiency may be asymptomatic, but may be severe, affecting mainly bones (osteomalacia, osteoporosis with increased risk of fractures) and muscles. Immune functions are also impaired resulting in increased risk to infections, autoimmune diseases and tumours.

III.2 Pharmacokinetics

The MAH has provided a adequate overview of the pharmacokinetics of vitamin D, including information on absorption, distribution, metabolism and excretion, drug interactions and other relevant non-clinical studies performed with animals and with human cells. The literature shows that concomitant use of thiazide diuretics may increase risk of hypercalcaemia. Some drugs, e.g. phenytoin or barbiturates, glucocorticoids, rifampicin, isoniazid, actinomycin and imidazole antifungals may reduce the effect of vitamin D. Excessive dosing of vitamin D can induce hypercalcaemia, which may increase the risk of digitalis toxicity

and serious arrhythmias due to the additive inotropic effects. Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil, may reduce the gastrointestinal absorption of vitamin D. Orlistat may potentially impair the absorption of cholecalciferol.

III.3 Toxicology

The MAH has provided an adequate overview of the toxicology of cholecalciferol based on literature. This included animal studies for acute toxicity, repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity and a discussion on the safety data of the excipients. There are no indications of carcinogenic potential for cholecalciferol. In contrast, the results of several early studies show that vitamin D deficiency increases the risk of several cancer (Grant, 2009) and that dietary calcium and cholecalciferol modulate tumorigenesis and apoptosis of cancer cells (Sitrin et al., 1991; Yang et al., 2008). The bioactive form of vitamin D_1 (25(OH)2D_3) has been shown to possess significant anti-tumour potential. More recent data indicate also that 1,25(OH)2D_3 also impacts energy utilisation in tumour cells (Abu el Maaty & Wölfl, 2017).

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol Acure is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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 data on these aspects.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance, no new clinical data was submitted, instead the MAH submitted a clinical overview for the justification of the proposed indications and posology, which includes numerous publications. This is acceptable.

IV.2 Pharmacokinetics

In accordance with part II of Annex I of Directive 2001/83, regarding article 10a applications, the MAH demonstrated using bridging data that the product applied for is similar to the

products described in literature. The MAH has provided a well summarised pharmacokinetics overview which is briefly described below. This is sufficient evidence to bridge the statements regarding the pharmacokinetics of cholecalciferol to the proposed formulations.

Absorption

Vitamin D is easily absorbed in the small intestine. Food intake potentially increases the absorption of vitamin D. The presence of bile is required for absorption, consequently the gastrointestinal absorption may be decreased in patients with hepatic, biliary, or gastrointestinal disease. Because vitamin D is fat soluble, it is incorporated into chylomicrons and absorbed via the lymphatic system. Approximately 80% of ingested vitamin D appears to be absorbed systemically through this mechanism, mainly in the small intestine.

Ilahi et al. (2008) characterised the time course and response of 25-hydroxyvitamin D [25(OH)D] or calcidiol. 40 healthy subjects with limited sun exposure were divided into two groups. One group of 30 subjects was supplemented with a single oral dose of 100.000 IU cholecalciferol. A second group of 10 subjects served as a control group to assess the seasonal change of calcidiol. Serum 25(OH)D concentrations were followed for 4 months. The highest achieved concentration was 64.2 ng/mL. The control group had a nonsignificant change from baseline of -0.72 ± 0.80 ng/mL during 4 months. Roth et al. (2012) conducted a pharmacokinetic study of single-dose vitamin D_3 supplementation in women of reproductive age. A single oral vitamin D_3 dose (70.000 IU) was administered to 34 non-pregnant and 27 pregnant women (27 to 30 weeks gestation). For all subjects the average 25(OH)D concentration was 19 nmol/L above baseline during the first month. The rate of rise was slightly slower in pregnant women. Supplementation did not induce hypercalcaemia, and there were no supplement-related adverse events. Cipriani et al. (2013) evaluated the long-term bioavailability and metabolism of a single oral (po) or intramuscular (im) high dose (600.000 IU) of D_2 or D_3. Participants were 24 subjects with hypovitaminosis D. Vitamin D metabolites were measured in serum. The areas under the curve (AUC) of 25(OH)D after D_3 were significantly higher than those after D_2. Serum 25(OH)D basal difference significantly increased at day 30 with po D_2 and D_3 and up to day 90 with po D_3. The im formulations produced a slow increased, and values peaked at day 120 relative to the other time points. $1,25(OH)_2D$ decreased at day 30 through day 120 while $1,25(OH)_2D_2$ increased at day 30 and up to day 120 after po D_2. Oral D_2 and D_3 produced increases in $24,25(OH)D_2$ and $24,25(OH)D_3$, respectively, at day 30. The potency of D_3 and D_2 is determined by the molecule's ability to raise 25(OH)D levels. Vitamins D_2 and D_3 have similar but variable metabolism due to differences in their chemical structure. According to a study (Armas et al., 2004) 50.000 IU dosage form of vitamin D_2 should be considered to be equivalent to no more than 15.000 IU of vitamin D_3 and perhaps closer to only 5.000 IU. The dosing of vitamin D_3 should take into account of endogenous vitamin D production and vitamin D intake by food, in particular if fortified with vitamins.

Distribution and biotransformation

Vitamin D is stored in both muscle and fat tissue, with vitamin D_3 levels in the serum correlated to the amount of D_3 in fat tissue. Studies of radioactively labelled D_3 find the whole body half-life of vitamin D_3 molecules to be about 62 days (Mawer et al., 1972). Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin (Haddad & Chyu, 1971).

Metabolism

Once absorbed from ingestion or produced in the skin, vitamin D_3 is released into the circulation where the majority is quickly hydroxylated in the liver. The product of this enzymatic modification, 25-hydroxyvitamin D_3 (25(OH)D), is the major circulating D_3 metabolite. The enzymes that catalyse the 25-hydroxylation of vitamin D are cytochrome P450- dependent enzymes. Studies over the past four decades in humans and a variety of animal species have shown that several cytochrome P450 enzymes (CYP2R1, CYP27A1, CYP3A4, CYP2D25 and possibly others), are capable of the 25-hydroxylation of vitamin D_3 and related compounds. These enzymes can be referred to as vitamin D-25-hydroxylases, with CYP2R1 emerging as the physiologically relevant enzyme. The second step of 1α-hydroxylation or the 25-OH-D_3-1α- hydroxylase is carried out by a single cytochrome P450 named CYP27B1. Inactive vitamin D_3 undergoes a sequential, two-step process to produce the hormonally active forms. The first step uses hepatic 25-hydroxylase enzymes to produce 25-hydroxyvitamin D_3 (25(OH)D). In the second step hydroxylation occurs by renal 1α-hydroxylase enzymes. Vitamin D hormone production is tightly controlled by factors such as serum calcium, phosphorus and intact parathyroid hormone. CYP24A1 catalyses the conversion of both 25(OH)D_3 and 1,25(OH)2D_3 into a series of 24- and 23-hydroxylated products targeted for excretion along well-established pathways culminating in the water-soluble biliary metabolite, calcitroic acid or a 26,23-lactone (Jones et al., 2014).

Elimination

Vitamin D disappears from plasma with a half-life ($t_{1/2}$) of 19 to 25 hours but is stored in fat depots for prolonged periods. The 25-hydroxy derivative has a biological half-life of 19 days. The primary route of excretion of cholecalciferol is the bile; only a small percentage of an administered dose is found in urine. 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 (HSDB, 2006).

Pharmacokinetics in Special Populations

Patients with Renal and Hepatic Impairment

chronic renal failure is characterised by diminished synthesis of, and resistance to, the active vitamin D metabolite 1,25(OH)2D_3, calcitriol. The results from Dasarathy et al. (2017) showed that daily supplementation with 2000 IU cholecalciferol for 6 months did not correct hypovitaminosis D in the majority of patients with non-alcoholic steatohepatitis (NASH). Further studies are needed to determine if higher doses are effective.

Children

No pharmacokinetic study has been performed in children. Clinical trials, measuring 25(OH)D levels after ingestion of various doses of vitamin D, found adequate absorption and bioavailability of oral preparations. The results from Lal et al. (2018) showed that weekly regimen of vitamin D supplementation of 60.000 IU is more effective than stoss regimen (60.000 IU single high-dose) for the treatment of hypovitaminosis D in children with chronic liver disease (CLD). Once normal levels are achieved, children should be shifted to 60.000 IU per month as maintenance dose.

Elderly
Studies on the intestinal absorption of vitamin in elderly have been performed, the results are inconsistent. It currently is unknown whether aging alters the gastrointestinal absorption of physiological amounts of vitamin D.

Effect of Race
Vitamin D insufficiency is common among darker skinned individuals. Non-Caucasians may require higher doses of vitamin D_3 supplementation to obtain sufficient serum levels despite adequate sun exposure. There are no data regarding racial differences in vitamin D absorption and/or metabolism. However, Cosman et al. (2000) showed that in response to $1,25(OH)_2D$ administration, black women had a slightly greater increase in serum calcium and greater decrement in parathyroid hormone (PTH). Community-dwelling black Americans, as compared with whites, had low levels of total 25-hydroxyvitamin D and vitamin D-binding protein, resulting in similar concentrations of estimated bioavailable 25-hydroxyvitamin D. Racial differences in the prevalence of common genetic polymorphisms provide a likely explanation for this observation (Powe et al., 2013).

Pharmacokinetic Interactions
Raimundo et al. (2011) compared serum 25-hydroxyvitamin D [25(OH)D] after oral intake of cholecalciferol with a high- or low-fat meal. A high-fat meal increased the absorption of vitamin D_3. The mean increase was larger, when the meal had at least 15 g of fat (Raimundo et al., 2014). Vitamin D_3 absorption from an oily solution was not influenced by the presence or absence of a meal (Cavalier et al., 2016). Excessive use of mineral oil, orlistat (Filippatos et al., 2008), cholestyramine or colestipol hydrochloride administration (Thompson & Thompson, 1969; Schwarz et al., 1980; Tonstad et al., 1996) may result in decreased intestinal absorption of vitamin D and analogues. Robien et al. (2013) concluded that clinical studies do not suggest that bile acid sequestrants alter vitamin D status. Actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting its enzymatic conversion (Bosmann & Chen, 1966; Henry et al., 1985). Rifampicin may reduce the effectiveness of vitamin D due to hepatic enzyme induction (Perry et al., 1982). Isoniazid may reduce the effectiveness of vitamin D due to inhibition of the metabolic activation (Brodie et al., 1981; Perry et al., 1982). Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D since the metabolism increases (Hahn et al., 1978). Vitamin D_3 exerts its actions through the vitamin D receptor (VDR), which is known to be an important regulator of P-glycoprotein (P-gp). While P-gp plays a significant role in limiting drug bioavailability,

vitamin D_3 supplementation (1000 IU per day) in human volunteers does not produce a P-gp-mediated drug interaction with orally administered digoxin (Kota et al., 2012).

Overall, the pharmacokinetics are adequately summarised by the MAH and a bridge between the new product and the different products used in the submitted literature has been established.

IV.3 Pharmacodynamics

The MAH has provided an extensive overview of general pharmacodynamic properties of cholecalciferol, which is acceptable.

In the body, vitamin D_2 and D_3 are converted to the main circulating forms called calcidiols ($25(OH)D_2$ or $25(OH)D_3$). It can be transformed into the biologically active metabolites called calcitriols ($1,25(OH)2D_2$ or $1,25(OH)2D_3$) (EFSA, 2016). The primary pharmacodynamics included the mechanism of action of vitamin D which has both genomic and nongenomic functions. For the genomic functions, the active form 1,25(OH)2D interacts with nuclear VDRs to influence gene transcription. Nuclear receptors for 1,25(OH)2D have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle and skin (epidermal cells and hair follicles), haematopoietic cells, lymphocytes, adipose tissue, and neurons. For the nongenomic functions, 1,25(OH)2D acts like a steroid hormone, working through activation of signal transduction pathways linked to VDRs on cell membranes. Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle. One of the major biological functions of vitamin D is to maintain calcium homeostasis which impacts on cellular metabolic processes and neuromuscular functions.

IV.4 Clinical efficacy

The MAH submitted many literature studies to support the proposed indication and has adequately discussed the clinical efficacy of cholecalciferol. Efficacy has been shown in clinical and subclinical vitamin D deficiency and insufficiency. Vitamin D in the food supply is limited and most often inadequate to prevent deficiencies. Supplemental vitamin D is likely necessary to avoid deficiency in winter months. However, all forms of vitamin D supplementation may not be equal in efficacy for maintaining optimal blood levels. A large number of vitamin D preparations of various strengths are available as over the counter (OTC) products and/or food supplements (Holick, 2017).

Dosing

The MAH recommends in the SmPC of this product a dose of one 20.000 IU capsule per week for a maximum of 4-5 weeks or one 25.000 IU capsule per week for a maximum of 4 weeks. This dose is in accordance with already registered SmPCs (e.g. NL/H/4811/004) and is therefore acceptable.

IV.5 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. The main adverse events by excessive intake of vitamin D are the development of hypercalcaemia or hypercalciuria. The precautions of use in special populations are sufficiently addressed in the SmPC.

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 Acure 20.000 IU and 25.000 IU.

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.7 Discussion on the clinical aspects

The clinical benefit of treating vitamin D deficiency is well known. The bibliographic data showed that vitamin D deficiency was resolved or improved as indicated by increases in serum calcidiol levels. The MAH discussed several studies to support the efficacy and safety of initial treatment of vitamin D deficiency with cholecalciferol. No new clinical studies were conducted. The proposed indication is widely used and known, and sufficiently discussed in the provided literature and therefore acceptable.

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 Cholecalciferol INVOS 20.000 IE and 25.000 IE soft capsules, (RVG 124697-8, NL/H/4811/001-005/DC) for content and to Genovita 1 mg (16/H/0127/001) for design and layout. 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 Acure 20.000 IU and 25.000 IU soft capsules has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the indications as well as the posology of the new product are in line with current cholecalciferol use and recommendations in the RMS and CMS countries, in which cholecalciferol has been registered for more than ten years. Based upon clinical data and the longstanding clinical experience, the use of cholecalciferol in the proposed indications can be considered well-established with demonstrated efficacy and safety.

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 Acure, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 25 October 2022.

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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
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