LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Divifarm
(Dry Vitamin D3 100 SD/S, cholecalciferol)

SE/H/2494/001

This module reflects the scientific discussion for the approval of Divifarm. The Public Assessment Report was written in Mars 2024 by the previous RMS (NL) after initial procedure (NL/H/5536/001/DC) and is attached at the end of this document. RMS transfer from NL to SE was completed 20 Feb 2024. For information on changes after this date please refer to the module 'Update'.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualify

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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol Meteor Trade 2000 IU film-coated tablets (cholecalciferol concentrate powder form)

NL/H/5536/001/DC

Date: 26 March 2024

This module reflects the scientific discussion for the approval of Cholecalciferol Meteor Trade 2000 IU film-coated tablets. The procedure was finalised on 12 April 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. LIST OF ABBREVIATIONS

1,25(OH)2D	1,25-dihydroxyvitamin D
1,25(OH)2D_3	Vitamin D_3
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
DBP	D-binding Protein
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
GI	Gastrointestinal
ICH	International Conference of Harmonisation
LD_{50}	Median Lethal Dose
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
WEU	Well-established Use

II. I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol Meteor Trade 2000 IU film-coated tablets, from Meteor Trade Kft.

The product is indicated for: treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/L) in adults.

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

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of cholecalciferol concentrate (powder form). For this type of 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. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Cholecalciferol concentrate (powder form) 2000 IU was first introduced into the European market at least ten years ago as a preoperative medication for the treatment of vitamin D deficiency.

The MAH submitted a justification for bridging between their product and the product used in the literature.

The concerned member states (CMS) involved in this procedure were Finland, Norway and Sweden.

III. II. QUALITY ASPECTS

III.1 II.1 Introduction

Cholecalciferol Meteor Trade is a film-coated tablet. The tablet is yellow coloured, round, biconvex and embossed with an 'S' on one side. Each film-coated tablet contains cholecalciferol (vitamin D_3) 2000 IU (equivalent to 50 mg vitamin D_3).

The excipients are:
Tablet core - lactose monohydrate, powdered cellulose (E460(ii)), modified food starch, maize starch, croscarmellose sodium (E468), sucrose, colloidal anhydrous silica (E551), magnesium stearate (E470b), sodium ascorbate (E301), medium chain triglycerides, and All-rac-αtocopherol (E307).
Film-coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), quinoline yellow aluminium lake (E104), and yellow iron oxide (E172).

The film-coated tablets are packed in opaque polyvinyl chloride/polyvinylidene chloridealuminium (PVC/PVdC-Alu) blisters and box.

III.2 II.2 Drug Substance

The active substance is cholecalciferol in the form of cholecalciferol concentrate (powder form), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water. Polymorphism is not known for cholecalciferol and is not a critical attribute in view of the manufacturing process of the cholecalciferol concentrate (powder form) where the active substance is dissolved. Furthermore, the powder flow is controlled as part of the drug substance specification.

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.

III.2.1 Manufacturing process

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

III.2.2 Quality control of drug substance

The active substance specification is largely in line with the Ph.Eur., with additional tests for identity and content of DL-α-tocopherol and sodium ascorbate in accordance with the CEP as well as additional in-house tests for powder flowability, water dispersibility, loss on drying and microbiological purity. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three production batches.

III.2.3 Stability of drug substance

The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

III.3 II.3 Medicinal Product

III.3.1 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 product has been developed as a new strength (line extension) of previously developed and marketed strengths. The 2000 IU product was manufactured as dose-proportional to the marketed 800 IU and 1000 IU strengths. Therefore, the formulation optimization studies have been described for the products already marketed. For the conclusions on well-established use, reference is made to the clinical overview. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

III.3.2 Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The main steps of the manufacturing process are blending, direct compression, film-coating and packaging. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

III.3.3 Control of excipients

The excipients comply with Ph.Eur. or in-house (Cellactose 80 and film-coating material) requirements. These specifications are acceptable.

III.3.4 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, dimensions, average weight, uniformity of mass, disintegration time, resistance to crushing, identification and assay of cholecalciferol and antioxidants, uniformity of dosage units and microbiological purity. Except for assay of cholecalciferol and antioxidants, the release and shelf-life requirements/limits are identical. The current specification is acceptable, in combination with the commitment to introduce a dissolution test post-approval. 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 provided. 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 from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

III.3.5 Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 25°C/ 60% RH (12 months), 30°C/65% RH (up to 12 months) and 40°C/75% RH (6 months). Furthermore, supportive stability data on three pilot scaled batches manufactured at the development site have been provided stored at 25°C/60% RH (30 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability data show a considerable decrease in cholecalciferol assay and content of sodium ascorbate during storage. Out-of-specification results were reported for appearance and assay of cholecalciferol after 6 months storage at accelerated conditions. No clear trends or changes were seen in the other tested parameters. All parameters remained in compliance with the shelf-life specification at long-term and intermediate conditions. The stability was tested in accordance with applicable European guidelines. Photostability studies performed on other strengths showed that the product is not stable when exposed to light and are considered representative for the 2000 IU strength.
On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'Do not store above 25°C', and 'Keep the blister in the outer carton in order to protect from light'.

III.3.6 Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the active substance and for the excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

The vitamin D_3 is prepared synthetically from a ruminant source material: cholesterol obtained from wool grease (lanolin) which is in compliance with EDQM Certificate of Suitability (CEP) according to Monograph No. 1483 on "products with risk of transmitting agents of animal encephalopathies".

III.4 II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol Meteor Trade has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Batch analytical data will be provided, including the results for dissolution testing. In addition, the available results of the dissolution testing for stability batches will be provided.
- A type IB grouped variation will be submitted, including the following:
    - addition of a new Site where Batch control /Testing takes place (B.II.b.2.a) o addition of a new specification of parameter to the release and shelf-life specification with its corresponding test method (B.II.d.1.c)
    - release limit: NLT 85% (Q) in 30 min
    - shelf-life limit will be derived from the results obtained from dissolution results in the ongoing stability batches.

IV. III. NON-CLINICAL ASPECTS

III.1 Introduction

IV.1 III.2 Pharmacology

The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D can be obtained from the diet and by the action of sunlight on the skin. Vitamin D_3 is produced in the skin by an ultraviolet light-induced photolytic conversion of 7-dehydrocholesterol to previtamin D_3 followed by thermal isomerisation to vitamin D_3 (Vasquez et al., 2004; Dusso et al., 2005). The active form of vitamin D_3 is 1,25–dihydroxyvitamin D_3 (1,25-(OH)2D3) and is formed following sequential hydroxylations in the liver and kidney (Dusso et al., 2005).

Most of the biological activities of 1,25-(OH)2D3 are mediated by a high-affinity receptor (vitamin D receptor, VDR) that acts as a ligand-activated transcription factor. The genomic and nongenomic actions of vitamin D combine to produce a multitude of responses in target cells (DeLuca, 2004; Norman, 2006; Walters, 1992; Malloy et al., 1999; Brown et al., 1999).

Vitamin D deficiency underlies the pathogenesis of rickets in children and osteomalacia in adults (DeLuca, 2004). 1,25-Dihydroxyvitamin D regulates calcium and phosphate metabolism via three target tissues: kidney, small intestine and bone. In the kidney, 1,25-dihydroxyvitamin D regulates calcium transport in the proximal tubule (Dusso et al., 2005); in the small intestine, it regulates calcium and phosphate uptake from the gut. 1,25-dihydroxyvitamin D is also involved in the maintenance of plasma calcium levels via bone resorption and formation. (DeLuca, 2004.) 1,25-dihydroxyvitamin D regulates the synthesis of PTH by a negative feedback mechanism. Subsequent investigations revealed that its deficiency and insufficiency, measured as serum 25-(OH)D of < 30 ng/mL (Henry, 2010), are associated with also nonskeletal diseases such as autoimmune diseases, inflammatory bowel disease, bacterial and viral infections, cardiovascular disease, cancer and neurocognitive disorders. Low vitamin D levels are also associated with increased risk of all-cause mortality (Welsh, 2017; Häusler & Weber, 2019; Sassi et al., 2018; Dusso et al., 2005).

It is recognised that 1,25D exerts non-genomic actions that are manifested, in the main, as the activation of signalling molecules, such as phospholipase C and phospholipase A2 (PLA2), phosphatidylinositol-3 kinase (PI3K) and p21ras, and the rapid generation of second messengers (Ca2+, cyclic AMP, fatty acids and 3-phosphoinositides such as phosphatidylinositol 3,4,5 trisphosphate), accompanied by the activation of protein kinases, such as protein kinase A, src, mitogen-activated protein (MAP) kinases, protein kinase C (PKC) and Ca2+-calmodulin kinase II (Hii & Ferrante, 2016). On the other hand, the metabolic, antiinflammatory and antifibrotic properties of vitamin D provide plausible mechanisms by which vitamin D may impact on the various steps of disease progression and severity. It has been known for some time that vitamin D has anti-proliferative and anti-fibrotic properties and plays an important role in the regulation of extracellular matrix, little has been known until recently about the effects of vitamin D on protection of liver cells (Kühne et al., 2014).

IV.2 III.3 Pharmacokinetics

Vitamin D is absorbed from the small intestine as bile salt-dependent micelles and circulated in the body via the lymph (Harris & Dawson-Hughes, 2002). Because of their unique physicochemical properties, bile acids are essential structural components of lipid micelles, and they are required for proper absorption of dietary lipids, including fat-soluble vitamins. In this capacity, bile acids promote the intestinal absorption of lipids and lipid-soluble vitamins (Schmidt et al., 2010).

Vitamin D is metabolised to the steroid hormone 1,25-dihydroxyvitamin D, a process which is promoted by parathyroid hormone (PTH). The hydroxylated metabolites 25(OH)D, 24,25(OH)2D, and 1,25(OH)2D are also lipophilic molecules. Because of their low solubility in the aqueous media of plasma, vitamin D compounds are transported in the circulation bound to plasma proteins. The most important of these carrier proteins is the vitamin D-binding protein (DBP). Only 5% of the total DBP of normal human plasma is occupied with vitamin D compounds. Therefore, under normal physiological conditions, nearly all circulating vitamin D compounds are protein bound, which has a great influence on vitamin D pharmacokinetics. DBP-bound vitamin D metabolites have limited access to target cells and are, therefore, less susceptible to hepatic metabolism and subsequent biliary excretion, which prolongs their halflife in circulation (Brown et al., 1999; Dusso et al., 2005). Albumin and lipoproteins are also important plasma carrier proteins with lower affinities for vitamin D metabolites than DBP. The first step in the metabolic activation of vitamin D3 is hydroxylation of carbon 25. This reaction occurs primarily in the liver, although other tissues including skin, intestine, and kidney have been reported to catalyse 25-hydroxylation of vitamin D (Boullata, 2010). The final cleavage product of 1,25(OH)2D3, calcitroic acid, is biologically inert (Brown et al., 1999; Dusso et al., 2005). Other polar metabolites of cholecalciferol have also been isolated, including 25,26 dihydroxycholecalciferol. A further metabolite may be produced in the kidney by 24-hydroxylation of 1,25(OH)2D3 to form 1,24,25(OH)3D3 (Coburn et al., 1974). There is also an enterohepatic recirculation of vitamin D and its metabolites, largely conjugated as glucuronides before secretion into the bile, and bile fistulae may thus lead to vitamin D depletion (Stamp, 1973; Kumar, 1990). Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months (Morrow, 2001). Metabolites are eliminated primarily (96%) through the bile and faeces (Expert Group, 2003).

IV.3 III.4 Toxicology

In animals chronic excess of vitamin D may cause hypercalcaemia, resulting in deposition of calcium in soft issues and bone demineralisation, anorexia, weight loss, anaemia, and weakness. In monkeys the cholecalciferol (vitamin D_3) was shown to be significantly more toxic than ergocalciferol (vitamin D_2) (Expert Group, 2003). At doses that far higher than the human therapeutic range, some level of teratogenicity has been observed in animal studies. Excess vitamin D during gestation in rabbits led to decrease foetal viability, increased number of abortions and induced supravalvular aortic lesions in the offspring (Chatterjee, 2011). High doses of vitamin D appear to affect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis. In rodents, administration of high levels of vitamin D during gestation results in retarded foetal and placental growth, loss of ossification of foetal bones and foetal skeletal degeneration. The doses in use, were significantly (in 2-4 orders) higher that that is in use of human, should be normalized when compared to human data. The results and doses with toxic signs or LD_{50} are clearly different in species. Therefore the nonclinical experimental data were inconsistent with the type of administration or duration of treatment, and interpolation to human may not be plausible to perform (Holick, 2011).

Our current understanding of the components of the vitamin D signal transduction machinery allows us to theorize in broad terms about how vitamin D toxicity might arise from hypervitaminosis D. Of the 3 hypotheses put forward to explain the triggering event for toxicity, increases in total 25(OH)D and free 1α,25(OH)2D concentrations are the most plausible, although they remain unproven (Jones, 2008). However, even in the absence of definitive evidence to establish the responsible metabolite, the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D is a good biomarker for toxicity, and the threshold for toxic symptoms is approximately 750 nmol/L (Jones, 2008; Expert Group, 2003). This threshold value implies that 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nmol/L, are safe and still leave a broad margin for potential medication error because values significantly higher than this value have never been associated with toxicity (Holick, 2011).

No genotoxicity was observed in studies *in vivo* or *in vitro*. No adverse effects were seen in results of the reported carcinogenicity studies involving cholecalciferol (Expert Group, 2003).

IV.4 III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol Meteor Trade 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.

IV.5 III.6 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 pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

V. IV. CLINICAL ASPECTS

V.1 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.

The MAH did not perform clinical pharmacology studies. The current application is based upon a well-established use application (Article 10a), i.e. it claims that cholecalciferol has a wellestablished medicinal use, with recognised efficacy and an acceptable level of safety on the basis of bridging to detailed scientific literature.

V.2 IV.2 Pharmacokinetics

Vitamin D_3 absorption is a non-saturable energy-independent process, is linear across a wide dosing range (Boullata, 2010). 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 (Harris et al., 1999; Holick, 2006; Vieth, 1999). Many vitamin D analogues are readily absorbed from the gastrointestinal (GI) tract following oral administration; the extent of GI absorption may be decreased in patients with hepatic, biliary, or GI disease (e.g., Crohn's disease, Whipple's disease, sprue).

In a human study, after subjects consumed orange juice fortified with 1000 IU vitamin D_3 daily for 12 weeks, serum 25(OH)D3 concentrations increased by 150%, and serum parathyroid hormone concentrations decreased by 25% compared with baseline; control subjects had a seasonal increase of 45% in 25(OH)D and no significant change in serum parathyroid hormone (Tangpricha et al., 2003). Another study with a daily consumption of cheese fortified with vitamin D3 (600 IU/day) demonstrated bioavailability. Younger (23 to 50 years) and older (72 to 84 years) adults had similar absorption. Among older individuals, this intervention was insufficient to increase serum 25(OH)D during limited sunlight exposure. A second study showed that vitamin D_2 was more bioavailable from cheese than from water, but there was no difference between older (72 to 84 years) and younger (23 to 50 years) individuals (Dabrowski et al., 2015). Fortification of milk with vitamin D_3 has also been successfully used in children aged 10 years to increase 25(OH)D3 level (Ginty & Prentice, 2004). Vitamin D absorption is impaired in patients with intestinal fat malabsorption syndromes, but there is little evidence of a general decline in fat absorption in healthy aging (Harris & Dawson-Hughes, 2002).

The metabolism of vitamin D consists of two steps; hydroxylation of carbon 25 and the formation of 1α,25-dihydroxyvitamin D [1,25-(OH)2D] from 25-hydroxyvitamin D (Dusso et al., 2005). The first step in the metabolic activation of vitamin D is hydroxylation of carbon 25, which occurs primarily in the liver. The second step in vitamin D bioactivation, the formation of 1α,25-dihydroxyvitamin D [1,25-(OH)2D] from 25-hydroxyvitamin D, occurs under physiological conditions, mainly in the kidney, but other cell types can contribute to circulating levels in specific conditions (pregnancy, chronic renal failure, sarcoidosis, tuberculosis, granulomatous disorders, and rheumatoid arthritis). Feedback regulation by 1,25(OH)2D3 limits its circulating levels to minimize the potential for vitamin D intoxication. Although the *in vivo* effects are due, in part, to increased calcium and phosphate and decreased PTH, direct suppression of 1α-hydroxylase activity has been noted in kidney cell culture. The regulation of 1α-hydroxylase at extrarenal sites is quite different from that of the renal enzyme, in keeping with the autocrine/paracrine functions of locally produced 1,25(OH)2D3. The rates of 1,25(OH)2D3 synthesis and degradation are under the control of local factors, i.e., cytokines and growth factors, that optimize the levels of 1,25(OH)2D3 for these cell-specific actions through mechanisms incompletely understood (Dusso et al., 2005).

Vitamin D and the hydroxylated metabolites 25(OH)D, 24,25(OH)2D, and 1,25(OH)2D are lipophilic molecule and are transported in the circulation bound to plasma proteins. The most important carrier protein is the vitamin D-binding protein (DBP). The relative affinities of vitamin D metabolites for DBP are estimated as 25(OH)D = 24,25(OH)2D > 1,25(OH)2D > vitamin D. The DBP is synthesized in the liver and circulates in plasma at concentrations 20 times higher than the total amount of vitamin D metabolites. Since the DBP has a single sterol binding site, it is estimated that only 5% of the total DBP of normal human plasma is occupied with vitamin D compounds. Therefore, under normal physiological conditions, nearly all circulating vitamin D compounds are protein bound, which has a great influence on vitamin D pharmacokinetics. The circulating albumin and lipoproteins are also important plasma carrier proteins with much lower affinities for vitamin D metabolites than DBP. Vitamin D

administered parenterally binds to both lipoproteins and DBP. However, lipoproteins are more efficient in the steps than DBP to carry the vitamin D_3 synthesized in the skin to the hepatocyte for 25-hydroxylation, whereas lymph chylomicrons mediate the intestinal absorption and hepatic uptake of the vitamin D ingested in the diet (Brown et al., 1999; Cooke & Haddad, 1989).

Vitamin D is principally excreted in the bile. It is also metabolised to water-soluble metabolites, such as calcitroic acid, and excreted in the urine. There is also an enterohepatic recirculation of vitamin D and its metabolites, largely conjugated as glucuronides before secretion into the bile, and bile fistulae may thus lead to vitamin D depletion (Kumar, 1990; Stamp, 1973). Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months. Metabolites are eliminated primarily (96%) through the bile and faeces (Stamp, 1973). The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life approximately 2 months). Its main transported metabolite, 25-hydroxyvitamin D(3) [25(OH)D(3)], shows a half-life of approximately 15 days and circulates at a concentration of 25-200 nmol/L, whereas the hormone 1α,25(OH)(2)D(3) has a half-life of approximately 15 hours (Jones, 2008).

V.3 IV.3 Pharmacodynamics

No new studies on PD have been conducted. The pharmacodynamics of cholecalciferol is wellestablished and has been adequately summarized by the MAH. No new data have been submitted, which is acceptable given the legal basis under which it has been submitted.

V.4 IV.4 Clinical efficacy

Supplementation with cholecalciferol is to be considered as well-established for the treatment of vitamin D deficiency. The MAH has adequately summarised the bibliographical efficacy data in the requested posology in the clinical overview.

V.5 IV.5 Clinical safety

The safety of cholecalciferol in the proposed indication and posology is considered wellestablished. The MAH has adequately summarised the bibliographical safety data in the clinical overview. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcemia and hypercalciuria are the main adverse events. The precautions of use in other special populations are sufficiently addressed in the SmPC.

V.6 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 Meteor Trade.

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.

V.7 IV.7 Discussion on the clinical aspects

This procedure concerns a well-established use application for cholecalciferol. For this authorisation, reference is made to literature. No new clinical studies were conducted. The pharmacokinetics of cholecalciferol can be considered well established. The bridge to the products used in the literature to claim WEU is established as adequate justification has been provided by the MAH. Risk management is adequately addressed. The clinical aspects of this product are approvable.

VI. 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 language used for the purpose of user testing the PL was Danish.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference Divisun tablets, 800 IU film-coated tablets, Mylan Healthcare B.V. (RVG 109770). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VII. VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol Meteor Trade 2000 IU film-coated tablets has a proven chemicalpharmaceutical quality Cholecalciferol is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Meteor Trade, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 2023.

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VII.2 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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er, chronological number and grouping qualifier (when applicable)