COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vitamine D3 Teva 5600 IU, soft capsules (cholecalciferol)

NL/H/5542/001/DC

Date: 26 November 2024

This module reflects the scientific discussion for the approval of Vitamine D3 Teva 5600 IU soft capsules. The procedure was finalised on 11 October 2023. 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 Vitamine D3 Teva 5600 IU, soft capsules, from Teva B.V.

The product is indicated for: prevention of vitamin D deficiency in adults with an identified risk, including patients with osteoporosis as an adjuvant to specific osteoporosis therapy.

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. 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 (vitamin D_3) was first introduced into the European market at least ten years ago as a preoperative medication for prevention of vitamin D deficiency in adults with an identified risk, including patients with osteoporosis as an adjuvant to specific osteoporosis therapy.

The MAH submitted an adequate clinical overview, which includes 198 references published up to year 2021. Efficacy and safety are supported by multiple literature studies and meta-analyses containing various formulations. Based on this data it can be expected that the current formulation will result in exposures that are comparable to the formulations in the literature. This rationale provided by the MAH is therefore considered sufficient substantiation for the bridge to literature.

The concerned member states (CMS) involved in this procedure were Germany, Luxembourg and Poland.

The MAH received the OTC (over the counter) status for this medicinal product. For the assessment of this request, the criteria as laid down in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use (European Commission, 2006 revision) apply, which consists of four criteria and other considerations. This is in line with the CMDh Best Practice Guide for authorisation of Non-Prescription Medicines in the Decentralised and Mutual Recognition Procedures. The four criteria and other considerations to classify a medicinal product as “subject to medical prescription” are described and weighed by the MAH. The MAH stated that Vitamine D3 Teva does not meet these criteria and therefore confirms that its product can be classified as “not be subject to medical prescription”.

II. QUALITY ASPECTS

II.1 Introduction

Vitamine D3 Teva is a red-brown, opaque, oval-shaped, soft capsule filled with clear, slightly yellow, oily liquid. It contains as active substance 0.140 mg cholecalciferol corresponding to 5600 IU vitamin D_3.

The excipients are:
Capsule fill: medium-chain triglycerides and all-rac-α-Tocopherol (E307).
Capsule shell: gelatine, glycerol (E422), iron oxide yellow (E172), iron oxide red (E172) and purified water.
Trace substances of phosphatidylcholine (from soybean), caprylic/capric triglycerides, ethanol, glyceride (from sunflower seed oil), oleic acid, ascorbyl palmitate and α-tocopherol.

The soft capsules are packed in PVC/PVdC-Aluminium (polyvinyl chloride/polyvinylidene chloride) blister packs.

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance are white or almost white crystals which are practically insoluble in water, freely soluble in ethanol (96%), soluble in trimethylpentane and in fatty oils. It is sensitive to air, heat and light. Solutions in solvents without an antioxidant are unstable and are to be used immediately. Particle size distribution is not relevant as the finished product is a liquid.

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. Two CEPs were submitted.

<u>Manufacturing process</u>
CEPs have been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. as well as the residual solvents test included in the CEPs. The drug product manufacturer also performs tests for microbiological quality.

Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance

Site I: The re-test period of 60 months is acceptable when stored under the stated conditions.
Site II: The active substance is stable for 36 months when stored under the stated conditions.
Assessment thereof was part of granting the CEPs (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 necessity of the antioxidant all-rac-α-tocopherol has been justified. Formulation trials were performed to evaluate the choice for a suitable antioxidant and a suitable lipid solvent. According to Ph. Eur., cholecalciferol is "practically insoluble in water". In the proposed formulation, cholecalciferol is dissolved in the medium-chain triglycerides in the formulation. As the active substance is already dissolved, there is no reason to perform dissolution testing on the finished product. Thus, it is acceptable that no dissolution test was developed. In addition, as cholecalciferol is "practically insoluble in water", there is no point in comparing dissolution profiles in physiological pHs, as required in the Bioequivalence Guideline, of the proposed formulation against other cholecalciferol products on the EU market or the products used in literature. Hence, it is acceptable that no dissolution study results are provided in the dossier. The MAH states that the disintegration test is performed in accordance with Ph. Eur. Overall, the pharmaceutical development of the drug product has been adequately performed.

Manufacturing process

The manufacturing process is a non-standard process involving capsule shell mass preparation and colouring, capsule fill solution preparation, encapsulation, drying, capsule polishing, visual sorting control, bulk packaging and final packaging into blisters. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

Most of the excipients comply with Ph.Eur. requirements. For the excipient, used as a band lubricant, an in house specification is provided and iron oxide red and yellow comply with regulation 231/2012/EC (colours used in foods). These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of cholecalciferol and α-tocopherol, uniformity of dosage units by mass variation, disintegration, water content, assay, α-tocopherol content, impurities and microbiological quality. 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 batches 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 batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No clear trends or changes were seen in any of the tested parameters at both storage conditions, except for out of specification results for appearance after 12 months storage at long-term conditions. The root cause has been adequately clarified and was not related to the quality of the drug product. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are 'Do not store above 25 °C. Store in the original package in order to protect from moisture'.

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 drug substance and gelatine 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vitamine D3 Teva 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 provided an extensive non-clinical literature overview based on public literature on the pharmacodynamics of cholecalciferol. Vitamin D, either produced from 7-DHC (pro-vitamin D3) in a nonenzymatic step under the influence of sunlight in the skin, or absorbed from the diet, is first metabolised to 25OHD and then to its active form 1,25(OH)2D (calcitriol) by cytochrome P450 mixed-function oxidases (CYPs). 1,25(OH)2D binds to its specific nuclear Vitamin D receptor (VDR), which in turn binds with the retinoic acid X receptor (RXR) to form

a heterodimeric complex. This complex interacts with specific sequences in the promoter region of vitamin D-responsive genes (VDRE) which in turn initiates the binding of several transcriptional factors that ultimately results in either an increased or decreased expression of vitamin D-responsive genes. Activation of VDR by 1,25(OH)2D promotes intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilisation from the bone. Once 1,25(OH)2D carries out its function in the small intestine, it then induces the expression of CYP24 which results in the initiation of a cascade of metabolic steps to biologically inactive excretory product, calcitroic acid (Bikle, 2014; Bikle 2020; Holick, 2002; Charoenngam et al., 2019).

Regarding secondary pharmacodynamics, it has been described that due to the wide distribution of VDR in most tissues and cells, vitamin D has multiple non-calcaemic actions. The activation of the VDR by 1,25(OH)2D results in a multitude of biologic activations in these tissues through both genomic and non-genomic pathways. 1,25(OH)2D has pro-differentiation and antiproliferation effects on the keratinocyte, antitumorigenic and antimetastatic activities on several types of cancer cells, immunomodulatory effects on macrophages and on activated T and B lymphocytes, effects on skeletal muscle function, and protective effects against cardiometabolic disorders and pregnancy related complications (Charoenngam et al., 2019).

No formal safety pharmacology studies according to ICH S7A/B with cholecalciferol have been performed or identified in public literature by the MAH. In view of the long history of use and the fact that cholecalciferol is a naturally occurring intermediary metabolite in humans, this is acceptable for the purpose of this well-established use application. In line with the pharmacological role of vitamin D the main adverse effect of vitamin D overdose in humans in hypercalcemia.

The MAH reported a small amount of non-clinical data on pharmacodynamic drug-drug interactions. Taking into account the substantial clinical experience, the pharmacodynamic drug interactions of cholecalciferol have been sufficiently addressed from a non-clinical perspective.

The primary, secondary and safety pharmacology, and pharmacodynamic drug interactions have been adequately discussed based on available literature for the purpose of a well-established use application.

III.2 Pharmacokinetics

Information provided by the MAH with respect to absorption is limited and is mostly related to the mechanism of distribution of vitamin D in the body. However, considering the long history of use and significant clinical experience with vitamin D, this can be accepted. Dietary cholecalciferol is absorbed in the small intestine from which it is carried by chylomicrons into lymph vessels and eventually into systemic circulation.

Information provided by the MAH in the distribution section describes mainly specific autoradiographic studies focusing on vitamin D distribution and receptor binding in predefined tissues and as such, is not very suitable to derive general conclusions on the

distribution of cholecalciferol in the body following its synthesis in the skin or dietary uptake. However, this information has been provided in the sections on primary pharmacology and absorption. Vitamin D3, obtained from the isomerisation of pre-vitamin D3 in the epidermal basal layers, or from intestinal absorption of natural and fortified foods and supplements, binds to vitamin D-binding protein (DBP) in the bloodstream, and is transported to the liver where it is hydroxylated by liver 25-hydroxylases. The resultant 25-hydroxycholecalciferol [25(OH)D] (calcifediol or calcidiol) is 1-hydroxylated in the kidney by 1α-hydroxylase. This yields the active secosteroid 1α,25-dihydroxyvitamin D3 (calcitriol, 1,25(OH)2D, 1α,25(OH)2D3), which has different effects on various target tissues. The part of vitamin D which is not catabolised, is stored in the adipose tissue (Holick, 2002; Dominguez et al., 2021).

As previously discussed, cholecalciferol is hydroxylated in the liver to 25(OH)D which is subsequently bioactivated primarily in the kidney to 1,25(OH)2D (calcitriol) which is the active form of vitamin D. The 25-hydroxylation of vitamin D can be accomplished by a number of enzymes, but the most important 25-hydroxylase is CYP2R1, while the renal CYP27B1 (25(OH)D3-lα-hydroxylase) is likely responsible for most of the circulating 1,25(OH)2D. Both 25OHD and 1,25(OH)2D are catabolised by CYP24A1. CYP24 is 25-hydroxyvitamin D3 24 hydroxylase (24(OH)ase) which hydroxylates both 25(OH)D3 and 1,25(OH)2D3 resulting either in calcitroic acid due to hydroxylation of 1,25(OH)2D3 or in 24,25(OH)2D3 due to hydroxylation of 25OHD (Bickle, 2014; Christakos et al., 2010). Information presented by the MAH on the metabolism of cholecalciferol is considered sufficient.

Vitamin D is excreted mainly in bile and faeces, whereas urinary excretion plays a minor role (Lorentzon and Danielsson, 1985). Information provided by the MAH on the excretion is limited but can be accepted in view of long history of use and substantial clinical experience.

The submitted literature data are sufficient to assess the non-clinical absorption, distribution, metabolism and excretion of cholecalciferol for the purpose of a well-established use application.

III.3 Toxicology

The toxicity of cholecalciferol is well known in humans and animals. As expected, the adverse effects in laboratory animals following cholecalciferol administration were driven by markedly increased calcium and phosphorus levels leading subsequently to organ and blood vessels calcification. Acute and chronic administration of excessive doses of cholecalciferol may lead to hypervitaminosis D manifested as hypercalcemia. In general, the results of hypervitaminosis D is calcification of soft tissues (Scientific Committee on Food, 2002).

Cholecalciferol gave consistently negative results across the panel of *in vitro* and *in vivo* tests, including the standard Ames, chromosome aberration and mouse lymphoma tests, and is considered not genotoxic (Mortelmans et al, 1969; Tugcu et al., 2021; Kitagaki et al., 1996).

Available animal data indicate that cholecalciferol causes proliferative changes in adrenals of rats, and phaeochromocytoma manifest in rats already after 26 weeks of exposure (Tischler et al., 1999). This effect is probably related to the altered calcium homeostasis causing

chromaffin cell proliferation in the adrenal medulla (Tischler et al., 1996). Cholecalciferol is not considered carcinogenic to humans.

Cholecalciferol is teratogenic at dose levels significantly exceeding normal endogenic levels. Extended hypercalcemia may adversely affect a developing unborn child, causing e.g. physical retardation and supravalvular aortic lesions (Scientific Committee on Food, 2002; McClain et al., 1980). Vitamin D3 and metabolites pass into the breast milk (Marya et al., 1991a; Marya et al., 1991b).

No literature studies on local tolerance are submitted by the MAH. Considering that cholecalciferol will be administered by oral route, this is acceptable.

No new studies have been submitted by the MAH. A public reference has been provided suggesting that vitamin D supplementation may improve the severity of atopic dermatitis (Tugcu et al., 2021).

The MAH has provided an adequate non-clinical overview of toxicity studies with cholecalciferol based on public literature, which is acceptable. The non-clinical overview on toxicology is sufficient for the purpose of a well-established use application.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Vitamine D3 Teva 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 pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview

justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

In general, the pharmacokinetics of cholecalciferol and (active) metabolites are sufficiently described. About 80% of a cholecalciferol dose administered is absorbed (Jones et al., 1998, Holick 2006; AHFS 2021; Jones et al., 2012). Cholecalciferol undergoes rapid metabolism in the liver by hydroxylation to 25-hydroxycolecalciferol via cytochrome P450 (CYP) enzymes. 25-hydroxycolecalciferol enters the circulation bound to its DBP and travels to the kidney, where megalin translocates the DBP-25(OH)D complex into the renal tubule and the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B) introduces a hydroxyl function on C-1 to form 1α,25-dihydroxyvitamin D [1,25(OH)2D] in the mitochondria. It is subsequently metabolised in the kidneys to 1,25-dihydroxycolecalciferol. 1,25-dihydroxycolecalciferol is the active metabolite and the major circulating form of vitamin D ((Kumar, 1984; Jones et al., 1998; Holick, 2007; Holick, 2009)).

Special populations

Information on the pharmacokinetics of cholecalciferol in male and female, different ethnic groups, elderly, renal impairment and children was included in the clinical overview.

Bridging to literature

A pharmacokinetic overview has been provided. Taking into account the comparison of the pharmaceutical form and ingredients of the product to be marketed and those mentioned in literature, it can be expected that the pharmacokinetics are comparable. Moreover, the proposed formulation does not contain critical excipients. Based on this, bridging to the product described in literature is considered sufficiently established.

IV.3 Pharmacodynamics

The pharmacodynamics of cholecalciferol are well-established and have been adequately summarised by the MAH. No new data are submitted, which is acceptable given this concerns a Well-established use application.

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.

Cholecalciferol is widely used and the effectiveness in the proposed indications is well known and sufficiently discussed in the provided literature. The prevention indication is considered acceptable. It is agreed with the MAH that vitamin D should be used as an adjuvant to the specific therapy for osteoporosis in adult patients who are at risk of vitamin D deficiency. In line with Article 71 of Directive 2001/83/EC, one of the criteria for a non-prescription status requires that a product can be used without medical supervision. Although the diagnosis of osteoporosis can only be done by a DEXA scan following consultation with a physician, it is a

common diagnosis in which it would be contributing if cholecalciferol would be available under over the counter (OTC) status for osteoporosis. Moreover, a dose of 5600 IU per week is not likely to cause any adverse event and does not require medical supervision. Next to this, "prevention of vitamin D deficiency in patients with an identified risk" also covers the indication "as an adjuvant to osteoporosis therapy in patients who are at risk of vitamin D deficiency".

The proposed dose of one capsule of 5600 IU per week is acceptable.

IV.5 Clinical safety

The safety of cholecalciferol in the proposed indication and posology is considered well-established. 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. Hypercalcaemia and hypercalciuria are the main adverse events. The precautions of use in other 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 Vitamine D3 Teva.

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

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.

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. T

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 25.000 IU soft capsules, NL/H/5149/001. 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

Vitamine D3 Teva 5600 IU, soft capsules has a proven chemical-pharmaceutical 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 essential similarity has been demonstrated for Vitamine D3 Teva 5600 IU, soft capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 October 2023.

LITERATURE REFERENCES

AHFS Drug Information (2021). Vitamin D Analogs General Statement, monograph From: Lexicomp® website [Accessed December 2021]

Bikle, D. D. (2014). Vitamin D metabolism, mechanism of action, and clinical applications. Chemistry & biology, 21(3), 319-329.

Bikle, D. D. (2020). Vitamin D: Newer concepts of its metabolism and function at the basic and clinical level. Journal of the Endocrine Society, 4(2), bvz038.

Charoenngam, N., Shirvani, A., & Holick, M. F. (2019). Vitamin D for skeletal and non-skeletal health: What we should know. Journal of clinical orthopaedics and trauma, 10(6), 1082-1093.

Cheng, J. B., Levine, M. A., Bell, N. H., Mangelsdorf, D. J., & Russell, D. W. (2004). Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proceedings of the National Academy of Sciences, 101(20), 7711-7715.

Christakos, S., Ajibade, D. V., Dhawan, P., Fechner, A. J., & Mady, L. J. (2010). Vitamin D: metabolism. Endocrinology and Metabolism Clinics, 39(2), 243-253.

Dominguez, L. J., Farruggia, M., Veronese, N., & Barbagallo, M. (2021). Vitamin D sources, metabolism, and deficiency: available compounds and guidelines for its treatment. Metabolites, 11(4), 255.

Holick, M.F. (2002) Vitamin D. Clinic Rev Bone Miner Metab 1, 181–20).

Holick, M. F. (2006). Resurrection of vitamin D deficiency and rickets. The Journal of clinical investigation, 116(8), 2062-2072.

Holick, M. F. (2007). Vitamin D deficiency. New England journal of medicine, 357(3), 266-281.

Holick, M. F. (2009). Vitamin D status: measurement, interpretation, and clinical application. Annals of epidemiology, 19(2), 73-78.

Jones, G. (2008). Pharmacokinetics of vitamin D toxicity. The American journal of clinical nutrition, 88(2), 582S-586S.

Jones, G., Strugnell, S. A., & DeLuca, H. F. (1998). Current understanding of the molecular actions of vitamin D. Physiological reviews.

Jones, K. S., Schoenmakers, I., Bluck, L. J., Ding, S., & Prentice, A. (2012). Plasma appearance and disappearance of an oral dose of 25-hydroxyvitamin D2 in healthy adults. British Journal of Nutrition, 107(8), 1128-1137.

Kitagaki, T., Oguma, Y., Yokota, F., Ono, M., Shirakawa, K., Nagata, M., & Konishi, R. (1996). A mutagenicity study of calcipotriol (MC903). The Journal of Toxicological Sciences, 21(SupplementII), 465-474.

Kumar, R. (1984). Metabolism of 1, 25-dihydroxyvitamin D3. Physiological reviews, 64(2), 478-504.

Lorentzon, R., & Danielsson, Å. (1985). The effects of different vitamin D-states on intestinal absorption of vitamin D3 and its metabolites in rats. Acta Physiologica Scandinavica, 123(4), 437-444.

Marya, R. K., Saini, A. S., Lal, H., & Chugh, K. I. R. A. N. (1991a). Effect of vitamin D supplementation in lactating rats on the neonatal growth. Ind. J of Physiol. Pharm, 35, 170-174.

Marya, R. K., Rathee, S., Lata, V., & Mudgil, S. (1981b). Effects of vitamin D supplementation in pregnancy. Gynecologic and obstetric investigation, 12(3), 155-161.

McClain, R. M., Langhoff, L., & Hoar, R. M. (1980). Reproduction studies with 1α, 25-dihydroxyvitamin D3 (calcitriol) in rats and rabbits. Toxicology and Applied Pharmacology, 52(1), 89-98.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., & Zeiger, E. (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environmental mutagenesis, 8(S7 S7), 56-119.

Scientific Committee on Food. (2002). Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin D. *European Commission.* SCF/CS/NUT/UPPLEV/38 Final.

Tischler, A. S., Powers, J. F., Downing, J. C., Riseberg, J. C., Shahsavari, M., Ziar, J., & McClain, R. M. (1996). Vitamin D3, lactose, and xylitol stimulate chromaffin cell proliferation in the rat adrenal medulla. Toxicology and applied pharmacology, 140(1), 115-123.

Tischler, A. S., Powers, J. F., Pignatello, M., Tsokas, P., Downing, J. C., & McClain, R. M. (1999). Vitamin D3-induced proliferative lesions in the rat adrenal medulla. Toxicological sciences: an official journal of the Society of Toxicology, 51(1), 9-18.

Tugcu, G., Charehsaz, M., & Aydın, A. (2021). Toxicological evaluation of ergocalciferol, cholecalciferol, and their metabolites by a category approach. Drug and Chemical Toxicology, 44(6), 661-667.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5542/001/P/001	Article 61 (3): to update the leaflet in line with SmPC	Yes	14-05-2024	Approved	N/A
NL/H/5542/001/IB/002	Change to in-process tests or limits applied during the manufacture of the finished product • Other variation	No	10-07-2024	Approved	N/A