COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Cholecalciferol Teva, 20.000 IU soft capsules (cholecalciferol)

# NL/H/5469/001/DC

# Date: 15 March 2024

**This module reflects the scientific discussion for the approval of Cholecalciferol Teva, 20.000 IU soft capsules. The procedure was finalised on 27 July 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

| | |
|---|---|
| $1,25(OH)_2D$ | 1,25-dihydroxyvitamin D / calcitriol (metabolite of vitamin D) |
| 25(OH)D | Calcifediol (metabolite of vitamin D) |
| 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 |
| IU | International Unite |
| $LD_{50}$ | Median lethal dose (lethal dose, 50%) |
| MAH | Marketing Authorisation Holder |
| nmol/L | Nanomol per litre |
| 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 |
| Vitamin | D receptor |
| WEU | Well-Established Use |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol Teva, 20.000 IU soft capsules, from Teva B.V.

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

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. It is a bibliographical application based on the well-established medicinal use of Cholecalciferol (vitamin $D_3$). 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 in oral dosage forms was first introduced into the European market more than ten years ago. It has been widely marketed and used for the treatment of vitamin D deficiency and has a recognised efficacy and an acceptable level of safety. Bridging data has been submitted to bridge between the proposed drug product and the products used in the submitted literature.

The concerned member states (CMS) involved in this procedure were Bulgaria, Estonia, Germany and Latvia.

# II. QUALITY ASPECTS

## II.1 Introduction

Cholecalciferol Teva, 20.000 IU are orange, opaque, oval-shaped, soft capsule filled with clear, slightly yellow, oily liquid. Each capsule contains 0.500 mg cholecalciferol, equivalent to 20.000 IU vitamin $D_3$.

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

*Capsule shell* - gelatine, glycerol (E422), titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), purified water and trace substances of phosphatidylcholine (from soybean), caprylic/capric triglycerides, ethanol, glyceride (from sunflower seed oil), oleic acid, ascorbyl palmitate and α-tocopherol.

The capsules are packed in Polyvinylchloride/Polyvinylidene chloride/Aluminium (PVC/PVDC-Al) unit-dose 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 consists of 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. 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. Batch analytical data demonstrating compliance with this specification have been provided for two batches of the production site (s).

Stability of drug substance

The active substance is stable for 3 or 5 years 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 necessity of the antioxidant all-rac- α -tocopherol and 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 a suitable lipid solvent. No dissolution data were provided, this is acceptable since the active substance is already dissolved on the finished product. In addition, as cholecalciferol is practically insoluble in water, comparison of dissolution profiles

in physiological pHs of the proposed formulation against other cholecalciferol products on the EU market or the products used in literature, as required by the Bioequivalence Guideline, are not deemed necessary. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The soft capsules manufacturing process involves capsule fill mass preparation, capsule shell mass preparation, encapsulation, drying, mechanical sorting, visual sorting, bulk packaging and final packaging into blisters. The manufacturing process is considered a non-standard process in view of the low unit content (< 2%) of cholecalciferol. Adequate process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines. In addition, a holding time of 12 months for the capsules stored in bulk packaging has been justified.

Control of excipients

All excipients comply with the current version of the Ph. Eur. except for iron oxide yellow and phosphatidylcholine which comply with the current version of the Ph. Eur. and in-house specification. 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 active substance, identification α-tocopherol, uniformity of dosage units by mass variation, disintegration, water content of the shell, assay (including pre-cholecalciferol), α-tocopherol content, impurities/degradation products and microbiological quality. Except for the test's disintegration, water content, assay and α- tocopherol content, 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 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 production scaled batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months). The batches were packed in PVC/PVDC//Alu blisters. No clear trends or changes were seen in any of the tested parameters at both storage conditions, except for out of specification (OOS) results for appearance after 12 months storage at long-term conditions. In addition, under the accelerated storage conditions, the capsules of all three batches were observed to deform and stuck to the blister or to the aluminium foil of the blister. The root cause has been adequately clarified and was not related to the quality of the drug product. Therefore, despite the OOS results, extrapolation of the available stability data is acceptable. The stability was tested in accordance with applicable European 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 2 years. The labelled storage conditions are "Do not store above 25 °C. Store in the original package, in order to protect from light and moisture. Keep blisters in the outer carton".

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 excipient 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 Cholecalciferol Teva, 20.000 IU 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 main role of vitamin D is to sustain the overall homeostasis of calcium and phosphorus in vertebrates (Uhl, 2018). Vitamin D, either produced from 7-dehydrocholesterol (7-DHC, pro-vitamin $D_3$) in a nonenzymatic step under the influence of sunlight in the skin, or absorbed from the diet, is first metabolised to 25(OH)D 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 retinoid X receptor (RXR) to form a heterodimeric complex (Bikle, 2014; Bikle, 2020; Holick, 2002). 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 (Holick, 2002). Activation of VDR by $1,25(OH)_2D$ promotes intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from the bone (Charoenngam et al., 2019). 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 (Holick, 2002). 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).

## III.2 Pharmacokinetics

Vitamin D can either be synthesized in the skin from 7-DHC by a non-enzymatic photochemical reaction (Uhl, 2018) or absorbed following the dietary intake in the small intestine from which it is carried by chylomicrons into lymph vessels and eventually into systemic circulation. In the blood stream it is bound to vitamin D-binding protein (DBP). 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 (Holick, 2002). The 25-hydroxylation of vitamin D can be accomplished by several enzymes, but the most important 25-hydroxylase is CYP2R1, while the renal CYP27B1 ($25(OH)D_3$-lα-hydroxylase) is likely responsible for most of the circulating $1,25(OH)_2D$ (Bikle, 2014). Both 25OHD and $1,25(OH)_2D$ are catabolized by CYP24A1 resulting either in calcitroic acid due to hydroxylation of $1,25(OH)_2D_3$ or in $24,25(OH)_2D_3$ due to hydroxylation of 25OHD (Bikle, 2014; Christakos et al., 2010). The part of vitamin D, which is not catabolized, is stored in the adipose tissue (Lim and Kim, 2014). Vitamin D is excreted mainly in bile and faeces, whereas urinary excretion plays a minor role (Lorentzon and Danielsson, 1985).

## III.3 Toxicology

After oral administration of cholecalciferol, the $LD_{50}$ values were 42 mg/kg, 42.5 mg/kg and 80 mg/kg in rats, mice and dogs, respectively (RTECS, 2007). The toxicity is caused by marked hypercalcemia which leads to calcification of the vital organs with subsequent organ failure (Roder & Stair, 1999). In humans, acute vitamin D toxicity is usually caused by doses of vitamin D above 10.000 IU/day, resulting in serum 25(OH)D concentrations over 150 ng/mL (Dominguez et al., 2021). 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 (Scientific Committee on Food, 2002).

*In vitro* and *in vivo* studies with cholecalciferol gave consistently negative results for genotoxicity. The test panel included the standard Ames-test, chromosome aberration and mouse lymphoma tests. Based on the results, cholecalciferol is considered not genotoxic (Kitagaki et al., 1996; Mortelmans et al., 1986; Tugcu et al., 2021).

The available animal carcinogenicity literature indicates that cholecalciferol causes proliferative changes in adrenals of rats, and phaeochromocytoma manifest in rats already after 26 weeks of exposure. This effect is probably related to the altered calcium homeostasis causing chromaffin cell proliferation in the adrenal medulla (Tischler et al., 1996; Tischler et al., 1999). Cholecalciferol is not considered carcinogenic to humans.

The MAH submitted a combined literature overview on fertility and developmental toxicity of cholecalciferol. The data show that 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 (Friedman & Roberts, 1966; McClain et al., 1980; Gezmish et al., 2010; Marya et al., 1991; Li et al., 2021; Chan et al., 1979).

### III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol Teva, 20.000 IU 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. 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 the Directive 2001/83/EC (Annex I, part II) regarding article 10a applications, the MAH has demonstrated, using bridging data, that the product applied for is similar to those described in the literature. The MAH has provided a well summarised pharmacokinetics overview, this is sufficient evidence to bridge the statements regarding the pharmacokinetics of cholecalciferol to the proposed formulations. The current formulation is a soft capsule with cholecalciferol in an oily solution. As indicated by the MAH, based on different sources of literature, an effect of vehicle on cholecalciferol absorption cannot be detected. In addition, the MAH provided an overview that compares the composition of Cholecalciferol Teva, with other products. A number of these products that have the same and/or similar composition (i.e., containing medium-chain triglycerides (MCT) and all-rac-α-tocopherol (E307), or containing other oily solutions). Based on this data, it is considered unlikely that the current formulations will result in exposures that are different from the formulations in the literature. This rationale provided by the MAH is therefore considered acceptable. Therefore, comparative dissolution data are considered not possible, as it is a (oily) solution formulation and dissolution experiments will be hampered due to the oily solution in an aqueous media.

The absorption, distribution, metabolism, excretion have been appropriately described by the MAH. Cholecalciferol is well absorbed from the intestine with bioavailability around 80%. 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, where in the mitochondria the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B) introduces a hydroxyl function on C-1 to form 1α,25-dihydroxyvitamin D [1,25(OH)2D] (Chen et al., 1993; Holick, 2005; Holick, 2007). 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 (EFSA, 2016; Kumar, 1984; Jones et al., 1998; Holick, 2007; Holick 2009). Colecalciferol and its metabolites are excreted in the bile and faeces, and to a lesser extent in urine (Avioli et al., 1967; AHFS, 2021). The process of biliary excretion is non saturable in a wide dose range (physiological-pharmacological) (Kumar, 1984).

## IV.3 Pharmacodynamics

The pharmacodynamics of cholecalciferol is well-established and has been adequately summarized by the MAH. No new data have been submitted, which is acceptable for this 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 for the proposed indication.

*Dosing* adults
Initial treatment of clinically relevant vitamin D deficiency.
Appropriate doses to be considered are in the range of 800-4000 IU/day or a weekly or monthly equivalent dose as also indicated for instance in NL SmPCs of the Benferol (NL/H/3500/001-004) and Will Pharma (NL/H/2963/001-006) products. The proposed dose of 20.000 IU per week is considered acceptable for the initial treatment of vitamin D deficiency. A lower maintenance dose should be considered after one month.

## 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. The SmPC as proposed is considered acceptable if amendments are made as requested.

## 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 Teva, 20.000 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

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 clinical benefit of treating vitamin D deficiency is well known. The bibliographic data submitted showed that vitamin D deficiency was resolved or improved as indicated by increases in serum 25OHD levels. The MAH submitted and discussed many studies to support the treatment of clinically relevant vitamin D deficiency. The safety profile of cholecalciferol is well-known. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia and hypercalciuria are the main adverse events. Both the pharmacovigilance plan and the risk management plan are considered 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 Teva 25.000 IU, soft capsules (RVG 126804, NL/H/5149/001/DC). 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 Teva, 20.000 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 indication 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 Teva 20.000 IU, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 July 2023.

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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 |
|---|---|---|---|---|---|
| - | - | - | - | - | - |