COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dekristol 25,000 IU hard capsules

(cholecalciferol)

NL/H/4347/001/DC

Date: 23 September 2020

This module reflects the scientific discussion for the approval of Dekristol 25,000 IU hard capsules. The procedure was finalised at 9 October 2019. 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
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
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 Dekristol 25,000 IU hard capsules, from Mibe GmbH Arzneimittel.

The product is indicated for the initial treatment of clinically relevant vitamin D deficiency in adults.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of cholecalciferol. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

There is ample evidence of extensive use of cholecalciferol medicinal products in the EU. A wide geographical distribution within Europe is documented. Regulatory experience in Europe is available for at least 10 years. According to European legislation, all these products have been monitored by pharmacovigilance methods. The degree of scientific interest in the use of vitamin D in the intended indications is reflected in the published literature. Pertinent publications are given in the clinical overview as well as the clinical summaries and include a series of review articles, textbook chapters, recommendations of scientific bodies with respect to the underlying conditions to be treated, dose requirements and safety margins.

The concerned member states (CMS) involved in this procedure were Belgium, Spain, Italy and Poland.

<u>Indication</u>
Initially the MAH was seeking approval of Dekristol for the following additional indication: *"As adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency*". During the application procedure, the indication was removed.

Withdrawal of the 50,000 IU strength
Initially the application included another strength: Dekristol 50,000 IU hard capsule. However, the submitted scientific clinical data (on pharmacology, efficacy and safety) was not considered to be supportive of a well-established use of high-dose Vitamin D treatment for the requested indication and posology. The MAH withdrew Dekristol 50,000 IU hard capsules from the application before finalisation of the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Dekristol is a hard gelatin capsule with an opaque yellow body and cap, filled with colourless to slightly yellow oily liquid. The capsules have a colourless band and contain 0.625 mg cholecalciferol (equivalent to 25,000 IU vitamin D3).

The hard capsules are packed in opaque, white PVC/PVdC blister packs.

The excipients are: medium-chain triglycerides, gelatin, colloidal anhydrous silica, titanium dioxide (E171), quinoline yellow (E104), butylated hydroxytoluene and FD&C yellow No.6 (E110).

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Cholecalciferol is a white to almost white, practically odourless crystalline powder. It is practically insoluble in water, freely soluble in ethanol (96 per cent) and soluble in trimethylpentane and in fatty oils.

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. Sheep wool is used in the manufacture of the active substance cholecalciferol. The CEP also confirm that the substance cholecalciferol meets the criteria described in the Ph. Eur. TSE monograph.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the CEP and monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 5°C (60 months) and 25°C/60%RH (6 months). Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

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 choice of excipients is justified and their functions explained.
The active substance is dissolved in medium-chain triglycerides. As the drug substance is already dissolved in medium-chain triglycerides, no comparative dissolution studies at physiological pHs are presented comparing the proposed product with other cholecalciferol products on the market. Also, the active substance is also practically insoluble in water. Hence, dissolution studies in aqueous conditions at physiological pH will not show any active substance dissolved. Consequently, it is acceptable that no dissolution studies are presented.

Manufacturing process
The manufacturing process consists of four main steps: manufacture of drug substance concentrate, manufacture of bulk solution, capsule filling and capsule sealing. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
Except for the shell excipients, the excipients comply with Ph.Eur. requirements where applicable. 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 appearance, disintegration time, uniformity of dosage units, average filling mass, identity, content, purity and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three batches from the proposed production site 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 (36 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to ICH stability guideline. On basis of the data submitted, a shelf life was granted of

36 months. The product should be stored in the original packaging in order to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The gelatin is derived from animal source. Scientific data and/or certificates of suitability issued by the EDQM 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 Dekristol 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 primary pharmacodynamics of vitamin D with respect to bone health has been examined in great detail. Low calcium diet and inadequate supply of vitamin D in experimental animals were related to a decrease in bone mineral density, e.g. in the lumbar spine, which is a meaningful target with respect to the human situation. The effects of calcium and vitamin D deficiency were reversible upon substitution therapy in experimental animals. Similar results were obtained in experimental osteoporosis. The observed decrease in bone mineral density was reversible upon administration of vitamin D. Recent studies in rodents show that in the context of vitamin D and dietary calcium depletion, osteomalacia occurs when both vitamin D and dietary calcium levels are markedly reduced and osteoporosis occurs with either a low calcium diet alone or when vitamin D status is low and dietary calcium is adequate. The control of intestinal calcium transport proteins by vitamin D have been thoroughly characterized as well as the control of the active metabolite of vitamin D3 in order to provide the maximum benefit to bone health and to avoid adverse effects.

Vitamin D is a genuine constituent of the human body and is involved in numerous physiological processes and regulations, e.g. cardiovascular health; form, function and metabolism of skeletal muscles; nervous system health and disease, anticancer actions of vitamin D, expression of genes. Calcitriol has pleiotropic effects through the vitamin D receptor and vitamin D responsive elements of many genes. In addition, rapid non-genomic effects through a membrane receptor and second messengers have been identified.

Two pharmacodynamic drug interactions are of established clinical importance. Both are related to the impact of vitamin D on serum calcium. Hypercalcaemia may occur as a consequence of concurrent administration of thiazide diuretics. Calcium may augment the toxicity of digitalis glycosides and cause arrhythmias and even cardiac death. No animal studies are available regarding these interactions; the evidence is based on clinical experience.

III.2 Pharmacokinetics

Pharmacokinetic characteristics of absorption, distribution, metabolism and excretion have been thoroughly studied over extended time periods and are well established. The increasing knowledge about pharmacokinetic characteristics has been compiled and evaluated in pertinent review articles and textbooks over the years. The most recent of these have been used in this overview to feature available pharmacokinetic information. Pharmacokinetics have been sufficiently elucidated to allow safe dosing of the to-be-marketed formulation in patients.

III.3 Toxicology

In rodents, a single dose of vitamin D is rather well tolerated as indicated by high median lethal dose data. There is a discrepancy between published vitamin D data for the non-rodent species, the dog. A median lethal dose of 80 mg/kg seems unlikely because other reports identify 10 or 13 mg/kg as a lethal dose. Apparently, dogs tolerate a single high dose of vitamin D3 less well than rodents. Experimental single-dose studies clearly identified clinical and histopathological signs of acute toxicity.

Repeated doses of vitamin D3 have been assessed in an explorative manner in a rodent and a non-rodent species. Daily doses ranged between 5,000 IU/kg and 400,000 IU/kg in rats and 440 – 40,000 IU/kg in rabbits. Treatment duration ranged between 4 days and 6 months. Targets of toxicity were discovered in these studies and include clinical signs, renal toxicity, and persistent calcification of blood vessels, especially those close to the heart.
Although studies identified important and clinically relevant targets of toxicity, a no-observed-adverse-effect level cannot be derived from these studies. Therefore, the calculation of a safety factor in comparison to the intended dosage of the to-be-marketed formulation in humans is not possible. However, this disadvantage is compensated by the availability of no-observed-adverse-effect levels based on human experience.

The Salmonella typhimurium test (5 strains) did not result in the demonstration of genotoxicity. Vitamin D is a genuine constituent of the animal and human body; the intended indications are related to states of deficiency; the daily dose is in agreement with European risk assessments. In addition, vitamin D3 has never been associated with an increased risk of cancer.

In an experimental study calcitriol inhibited the metastasis of lung cancer in a VDR (-/-) mouse model. Current knowledge about vitamin D3 and its active metabolite calcitriol does not support a tumorigenic effect.

Several studies addressed the reproductive toxicity of vitamin D_2 or calcitriol in rats and rabbits. Probably none of the studies fulfilled GLP requirements. The study designs were not in agreement with current ICH guidance. A plethora of experimental conditions was used, e.g. exposure only before mating or exposure before mating until weaning, or exposure only in the last 6 days of pregnancy. Despite of all these drawbacks, a rather clear picture of reproductive toxicity evolved. Study results demonstrated the consequences of vitamin D deficiency. A physiologically satisfying supply is required for normal development of the offspring and the maintenance of maternal health. The impact of excess vitamin D exposure in pregnancy was examined in rabbits. Excess vitamin D had a deleterious impact on the life of mothers and offspring. There was a dose-dependent lethal toxic effect. Surviving dams and offspring demonstrated signs of vascular toxicity, notably supravalvular aortic stenosis in the offspring. Calcification of vascular tissue in dams and offspring is probably an expression of excess pharmacodynamics of vitamin D rather than a specific teratogenic effect.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The active pharmaceutical ingredient cholecalciferol is a vitamin which, due to its nature is unlikely to result in a significant risk to the environment. In addition, the preparation of Dekristol, is based on well-established medicinal use within the Community for at least ten years. It is therefore not expected to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

The application for Dekristol is based on well-established use. This is endorsed, since cholecalciferol has been registered for this indication for a long time and the dose is not increased. 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 Pharmacokinetics

Vitamin D is absorbed from the small intestine by passive diffusion. Most of the vitamin appears first within chylomicrons in lymph. Bile is essential for adequate absorption of vitamin D, deoxycholic acid is the major constituent of bile in this respect.
The MAH did provide reasoning why the pharmacokinetics of cholecalciferol can be bridged to the proposed formulation of Dekristol.
The capsules contain cholecalciferol as a solution in oil. Such formulations are not new. Data is submitted in which a comparable bioavailability was observed between tablet formulations and oily formulations. The MAH sufficiently demonstrated that the bioavailability of cholecalciferol is not affected when dissolved in medium-chain triglycerides, and therefore it can be considered demonstrate that the product applied for is similar to the products described in literature

IV.2 Pharmacodynamics

The MAH provided 5 pharmacodynamic studies from 1998 to 2013. The dose range of vitamin D in pharmacodynamic studies ranged between 500 IU/day and 50,000 IU/month, one study included a loading dose of 500,000 IU cholecalciferol. All studies reported expected and desired pharmacodynamic effects of cholecalciferol. There is a striking difference in baseline 25OHD levels perceived as deficient between 1996 and 2009/2013 with increasing values over time. More recent studies adopt higher doses of cholecalciferol especially in frail elderlies in order to correct vitamin D deficiency quicker. None of the studies reported safety problems, e.g. hypercalcaemia. The comparison of studies indicates that the treatment of vitamin D deficiency can be achieved with a wide variety of doses and dose regimens.

IV.3 Clinical efficacy

The MAH applied for the following indications:

- Treatment of vitamin D deficiency [serum 25-hydroxycalciferol (25OHD) < 25 nmol/l]
- Prevention of vitamin D deficiency in high-risk patients
- As adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency (25,000 IU capsules only)

Treatment and prevention of vitamin D deficiency
Fourteen studies focussing on patients with 25,000/50,000 IU or multiples thereof, given weekly or monthly were presented in the clinical overview. The observation period of studies is between 12 weeks to 1 year. Eight trials had a double-blind, placebo controlled, randomised design, one study had a blinded, randomised, placebo-controlled design. One trial was a randomised, double-blind, dose-response trial. Four trials had an open-label design with

either staggered ascending doses or comparative use of different formulations/doses of cholecalciferol.
The studies were categorised by the MAH as studies for initial treatment and used a variety of dosing schedules to investigate to achieve normal 25(OH)D levels after a certain period of treatment including loading doses and/or several weeks or months of treatment.
Appropriate doses to be considered are in the range of 800-4,000 IU/day 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.

To support the indication and posology of prevention of vitamin D deficiency, the MAH submitted two studies using dose levels of 50,000 to 100,000 IU/month for several months. In the first study, more than 40% of the patients were deficient in vitamin D questioning whether this study provides sufficient support for a prevention of vitamin D.
Additionally, it is demonstrated that even a dosage of 50,000 IU/week administered over a period of 16 weeks is effective and safe. The use of high dosage forms is only recommended during initial treatment phase, a lower dose should be use for maintenance.
The indication was changed to: "*for the initial treatment of clinically relevant vitamin D deficiency in adults*". This indication has been accepted.

Osteoporosis
Seven studies were described, these studies enrolled adults as well as elderly women and men and patients of very old age (>72 years). Studies in postmenopausal women included middle-aged adults or elderlies. One study had a randomised, double-blind, placebo-controlled, parallel group design. Three studies had a randomised, double-blind, comparative design. Two studies had an open, randomised, parallel group design. The submitted studies primarily investigated the efficacy based on 25OHD level, while one study of also studied the effects of supplementation with 800IU vitamin D3 and calcium on the frequency of hip fractures and other nonvertebral fractures in osteoporosis. Further, several meta-analyses investigated the reduction of the risk of fractures among elderly patients.

However, the indication has been removed as the published data of European studies in osteoporotic patients with vitamin D deficiency or at risk of vitamin D deficiency, treated concurrently with specific osteoporotic therapy was not considered to be sufficiently supportive for this indication.

IV.4 Clinical safety

The safety evaluation of orally administered cholecalciferol is based on the efficacy trials presented and on publications and textbook articles as well as documents from official bodies (e.g. WHO, Bundesinstitut für Risikobewertung, European Food Safety Authority).

A total of 4293 subjects participated in efficacy and safety trials; a total of 2474 subjects were exposed to cholecalciferol; 1819 were treated with placebo. The mean duration of trials

ranged between 12 weeks and 3 years. Intermittent administration included weekly and monthly dosing intervals. Total exposure to vitamin D ranged between 89,000 IU within 16 weeks and 876,000 IU within 36 months. Results of the trials presented were adequately summarised in tables and discussed separately in more detail.

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.

IV.5 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 that Dekristol.

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.6 Discussion on the clinical aspects

Dekristol is considered widely established. For this authorisation, reference is made to clinical studies and experience with cholecalciferol. Cholecalciferol has been shown to be effective for the initial treatment of clinically relevant vitamin D deficiency in adults. The provided clinical overview is sufficient. No new clinical studies were conducted.

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 test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dekristol 25,000 IU hard capsules has a proven chemical-pharmaceutical quality. Dekristol is an effective drug, which is considered widely established.

The benefit/risk balance is considered positive. It was shown that all vitamin D products described in the submitted literature have similar pharmacokinetic and pharmacodynamic characteristics with respect to the exposure to the main serum vitamin D metabolite and no significant differences in efficacy. Therefore, it can be concluded that the product to be registered is considered similar to the products described in the literature on which this well-established use procedure is based

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 Dekristol, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 October 2019.

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/4347/1/IB/001	Change in the trade name (invented name) of the finished product in Italy.	No	27-12-2019	Approved	-