CBG MEB

Public Assessment Report

Scientific discussion

Colecalciferol Benferol 25,000 IE, 50,000 IE and 100,000 IE soft capsules

(cholecalciferol)

NL/H/3500/001-003/DC

Date: 19 April 2017

This module reflects the scientific discussion for the approval of Colecalciferol Benferol 25,000 IE, 50,000 IE and 100,000 IE soft capsules. The procedure was finalised on 23 February 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BUN	Blood Urea Nitrogen
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet Light
VDR	Vitamin D receptor

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Colecalciferol Benferol 25,000 IE, 50,000 IE and 100,000 IE soft capsules, from Consilient Health Limited.

The product is indicated:

- for prophylaxis and treatment of vitamin D deficiency in adults and adolescents with an identified risk.
- in addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency, preferably in combination with calcium.

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

Marketing authorisations for different types of cholecalciferol oral dosage forms (tablets, drops, film-coated tablets) have been issued in most European countries since decades. Consilient Health Limited has decided to develop capsules containing 800 IU cholecalciferol.

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

The application is based on article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of cholecalciferol.

II. QUALITY ASPECTS

II.1 Introduction

Colecalciferol Benferol 25,000 IE is a light red, oval-shaped, soft capsule. It contains a slightly yellow oily liquid. Each capsule has “25” printed in white ink.

Colecalciferol Benferol 50,000 IE is a red, oval-shaped, soft capsule. It contains a slightly yellow oily liquid. Each capsule has “50” printed in white ink.

Colecalciferol Benferol 100,000 IE is an orange, oval-shaped, soft capsule. It contains a slightly yellow oily liquid. Each capsule has “100” printed in white ink.

Each capsule contains cholecalciferol 25,000 IE, 50,000 IE or 100,000 IE, equivalent to 0.625 mg, 1.25 mg or 2.5 mg vitamin D_3.

The capsules are packed in PVDC/Aluminium foil blisters.

The excipients are:
Capsule fill - All-Rac-α-tocopherol (E307) and medium chain triglycerides
Capsule shell – glycerol, gelatine, medium chain triglycerides, Allura Red AC (E129) and Sunset Yellow FCF (E110) (100.000 IE only)
Printing ink - Shellac (E904), titanium dioxide (E171) and simethicone

II.2 Drug Substance

The active substance is cholecalciferol, a well-established active substance described in the European Pharmacopoeia (Ph.Eur.). Cholecalciferol is a white to almost white, practically odourless crystalline powder. It is soluble in ethanol 96%, ether, chloroform and acetone, and practically insoluble in water. Several forms of cholecalciferol are described in the Ph.Eur. The drug substance form used in the product is the oily form. The oily concentrate is also described in the Ph.Eur.

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
The drug substance is obtained from crystalline cholecalciferol. The manufacture of cholecalciferol crystalline is covered by the CEP. Sufficient details have been provided on the manufacturing process.

Quality control of drug substance
The specification is in conformity with the monograph in the Ph.Eur. on cholecalciferol concentrate (oily form), with additional tests for identification and assay. Impurities and the anti-oxidants are routinely tested by the manufacturer. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three different batches stored at 15°C (36 months), 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Slight increases were observed in the peroxide value. Results remained within specification limits. A retest period is not required as the manufacturer will be testing every batch prior to use of the drug substance in the finished product manufacture.

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. Trial formulations using differing oils were evaluated. The choice of medium chain triglycerides is suitable for the oil to be used as the carrier of cholecalciferol. The required level of anti-oxidants was established. The overage of 5% is acceptable. Dissolution tests for cholecalciferol are not possible due to the non aqueous, fatty oil matrix in which the active substance is dissolved. Although the active substance itself is insoluble in water, confirmation has been provided that the dosage form complies with the specification of the Ph.Eur. disintegration test. The pharmaceutical development, including the selection of packaging materials and manufacturing process of the product, has been adequately performed.

Manufacturing process
The gelatine for the soft capsule is prepared in three stages. The encapsulation process is sufficiently described. Based on the low active substance concentration, the manufacturing process is non-standard. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for thee commercial scaled batches.

Control of 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, uniformity of dosage units, disintegration time, peroxide value, impurities, vitamin E assay, vitamin D_3 assay 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 from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three production scale batches of each strength stored at 25°C/60% RH (12 months for the 25.000 IE and 50.000 IE strengths and 9 months for the 100.000 IE strength), at 30°C/75% RH (9 months for the 25.000 IE and 50.000IE strengths and 6 months for the 100.000 IE strength), and at 40°C/75% RH (6 months). The batches were stored in the proposed blister packs. The conditions used in the stability studies are according to the ICH stability guideline. No significant trends are seen and the results are well within specification at all storage conditions. Based on the stability data provided the granted shelf-life is 18 months if stored in PVDC/Aluminium foil blisters not above 25°C. Photostability studies showed that the product is not stable when exposed to light. Therefore the storage condition "Keep the blisters in the outer carton to protect from light" is applied.

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

The gelatine 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 Colecalciferol Benferol 800 IE 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

Vitamin D is the product of a cholesterol-like precursor (7-dehydrocholesterol) after it has been irradiated by ultraviolet light (UV). The most well-known effect of vitamin D is maintenance of normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. In addition vitamin D has widespread effects on cellular differentiation and proliferation, can modulate immune responsiveness, and central nervous system function and may act as a chemo preventive agent against several malignancies including cancers of the prostate and colon.

III.2 Pharmacokinetics

Vitamin D is either obtained by UV radiation of the skin, or provided via food. Absorption of ingested vitamin D occurs with the aid of bile salts primarily in the lower third of the small intestine. Vitamin D enters the lymphatic system and then the blood stream. Further transport of vitamin D occurs through the lymph where the ingested vitamin is carried in the chylomicron fraction to the liver. As time passes, vitamin D increasingly associates with α2-globulins, to which it is tightly bound. Vitamin D_3 originating from the photolysis reaction occurring in the skin is directly transported into the liver by the vitamin D binding protein.

Vitamin D is typically located in 4 organs: the liver, as free vitamin D, the mucosa of the small intestine, the bone, and the first third of the kidney proximal tubule, but it has been shown that vitamin D is also present in nuclei of neurons in adult rat and mouse brains. Calcidiol is stored in the liver. Lesser amounts are distributed to adipose tissue and stored as vitamin D_3 at these sites for later release into the circulation. The half-life of vitamin D in adipose tissues is about 2 months. Calcidiol shows a half-life of 15 days whereas calcitriol shows a half-life of approximately 15 hours. The vitamin D receptor (VDR) has been found in over 36 cell types where it is thought to initiate physiological responses.

Vitamin D needs to be metabolised first in the liver to calcidiol and subsequently in the kidneys to become calcitriol, the biologically active form. In the liver, this hydroxylation is mainly carried out by two enzymes in the rat, one found in the microsomes and the other in the mitochondria of hepatic cells. Not lonely is this hormone produced in the kidneys as previously though. It has been demonstrated that it is produced in over 10 extra renal organs. Further hydroxylation occurs prior to elimination. Many metabolites of vitamin D_3 have been isolated from plasma.

The elimination of vitamin D metabolites occurs in the urine and faeces.

III.3 Toxicology

The toxic action of vitamin D is usually attributed to a disturbance of whole-body calcium homeostasis. However, in acute studies the animals die before hypercalcemia develops so the action may be mediated by a noxious effect of the vitamin D metabolite on essential cell functions. The mechanism of the lethal action of the vitamin D is still uncertain.

The major findings in repeated toxicity studies in rats, dogs and monkeys resulted from hypercalcemia and subsequent calcium deposits noted in the eyes, heart, kidney, lung and salivary glands. In humans, an excess in vitamin D will also present in hypercalcaemia, hypercalciuria, as well as increased serum calcidiol concentrations.

Vitamin D was tested negative for genotoxic potential in the Ames test and a micronucleus assay.
It is an endogenous substance produced naturally by contact of the skin by UV, therefore any cancer potential risk from this replacement therapy is not expected to exceed that of a population with normal vitamin D level.

Overdoses of vitamin D should be avoided during pregnancy as permanent hypercalcemia has been related to adverse effects on the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans.

III.4 Ecotoxicity/environmental risk assessment (ERA)

According to the note for guidance on the environmental risk assessment of medicinal products for human use (CPMP/SWP/4447/00), the MAH has provided an analysis of the Predicted Environmental Concentration (PEC) value of cholecalciferol. As the $PEC_{surface\ water}$ is below 0.01 µg/l, the medicinal product is unlikely to represent a risk to the environment following its prescribed usage in patients.

III.5 Discussion on the non-clinical aspects

The application for Colecalciferol Benferol 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 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

The MAH presented literature demonstrating cholecalciferol administered over a 4-week period produced a similar mean increase in calcitriol concentration, either from fish oil capsules or multivitamin tablet. Furthermore, the MAH presented a systematic review concluding no critical differences were highlighted among different nutritional and pharmaceutical preparation with regard of the absorption of vitamin D.

The composition of the pharmaceutical preparation is similar with regard to components that have already been applied in other products. It is therefore not expected to cause significant difference in absorption.

All vitamin D products described in the submitted literature have similar pharmacokinetic/ pharmacodynamic characteristics with respect to the exposure to the main serum vitamin D metabolite and no significant differences in efficacy.

The MAH has sufficiently supported that no differences in bioavailability are expected. Therefore, it can be concluded that Colecalciferol Benferol is considered similar to the products described in the literature on which this well established use procedure is based.

IV.3 Pharmacodynamics

The MAH has provided an overview of general pharmacodynamic properties of vitamin D. The pharmacodynamic section is considered sufficiently described. Section 4.5 of the SmPC reflects most of the interactions of vitamin D with other medicinal products. The interactions with orlistat, actinomycin, imidazole have also been added.

IV.4 Clinical efficacy

In order to demonstrate the efficacy of a dose of 800 IU per day of vitamin D in the indication "Prophylaxis and treatment of vitamin D deficiency in adults and adolescents with an identified risk and in addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency", the MAH has provided numerous publications. From the results of these studies, the efficacy of vitamin D 800 IU per day has been demonstrated in these proposed indications in adults. It is agreed that the results of the studies show that vitamin D is efficacious at the proposed dose.

The MAH has provided the results of 11 studies performed in children and/or adolescents. A wide range of doses was applied, varying from daily administration of 400 IU to 100,000 IU every 2-3 months. Studies were performed in healthy teenagers, human immunodeficiency virus (HIV) infected children, obese adolescents and subjects with cystic fibrosis. In all studies a rise in calcitriol was measured, and no safety issue occurred. The proposed posology is 800 IU daily, which is the common posology in line with other vitamin D products for adolescents. Therefore, the posology is considered acceptable for adolescents.

IV.5 Clinical safety

Based on the bibliographic data on clinical studies provided by the MAH, the safety of the capsules containing cholecalciferol 800 IU can be considered well-established. In addition, cholecalciferol has been found to be safe at higher doses than the proposed dose (800 IU). No issue concerning safety with Cholecalciferol Benferol 25.000 IE, 50.000 IE and 100.000 IE is expected.

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 Colecalciferol Benferol 25,000 IE, 50,000 IE and 100,000 IE.

Summary table of safety concerns as approved in RMP:

Important identified risks	None
Important potential risks	• Overdose (including hypercalcaemia, hypercalciuria & hypervitaminosis D)
Missing information	None

As there are no safety concerns associated with cholecalciferol there are no risk minimisation measures to describe.

IV.7 Discussion on the clinical aspects

Colecalciferol Benferol is considered widely established. For this authorisation, reference is made to clinical studies and experience with cholecalciferol. Cholecalciferol has been shown to be effective in the treatment of vitamin D deficiency and bone loss. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

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 with two participants, 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Colecalciferol Benferol 25,000 IE, 50,000 IE and 100,000 IE soft capsules has a proven chemical-pharmaceutical quality. Colecalciferol Benferol is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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 Colecalciferol Benferol, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 February 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Minor changes to an approved test procedure.	NL/H/3500/ 1-3/IA/001	IA	11-10-2016	4-11-2016	Approval	No