LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bencium
calcium carbonate
cholecalciferol concentrate (powder)

SE/H/1777/01-02/DC

This module reflects the scientific discussion for the approval of Bencium. The procedure was finalised on 2018-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Consilient Health Limited has applied for a marketing authorisation for Bencium (CalciBen), Chewable tablet, 500mg / 800 IU and 500mg / 2000 IU, Calcium / colecalciferol (vitamin D3. The active substance is Calcium carbonate, colecalciferol (calcium-vitamin D_3-supplement, it is used to treat lack of calcium and vitamin D deficiency).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, Pharmacokinetics and Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of calcium and vitamin D are well-known and text-book knowledge. Products containing calcium and vitamin D have been available in the EU for more than 20 years and their use is well-established with recognised efficacy and acceptable safety. The dose levels are within the dosage range used in clinical practise. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. No further studies are required and the applicant provides none.

III.2 Ecotoxicity/environmental risk assessment

Calcium and vitamin D are natural substances, the use of which will not alter the concentration or distribution of the substances in the environment. According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00) an ERA is not required for vitamins or electrolytes since they are unlikely to result in significant risk to the environment. The absence of an environmental risk assessment is thus considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol (vit D3), undergoes a biotransformation into 1,25 dihydroxycholecalciferol, a main active metabolite of vitamin D, which is necessary to promote the intestinal absorption of calcium. Calcium and vitamin D have a number of physiological functions particularly in bone mineralization. Calcium and vitamin D have a synergic effect.

Several Medicinal products containing cholecalciferol and/or carbonate calcium are authorized in EU Member States for prevention and treatment of vitamin D and calcium deficiency; and as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

IV.2 Pharmacokinetics

There is no pharmacokinetic data specific for the currently applied product, which is acceptable. Due to the nature of the active substances, it is not considered necessary to compare the bioavailability of calcium and vitamin D from the new product with that from existing products on the market. The product is intended to be a complement to dietary calcium and vitamin D3, which might be highly variable, and a potential minor difference in in vivo release properties from two different dosage forms would not be expected to lead to a different therapeutic profile. Moreover, as the absorption of calcium and vitamin D3 is controlled by a number of physiological processes and factors, the true absorption of these partly endogenous substances may be difficult to determine in a bioavailability study.

IV.3 Pharmacodynamics

Cholecalciferol (vitamin D3) is a liposoluble pro-hormone formed in the skin on exposure to UV light and converted into its biologically active form, 1,25-dihydroxycolecalciferol, in two

hydroxylation steps, first in the liver (position 25) and then in the renal tissue. Vitamin D is required to maintain normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralization of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D achieves this after its conversion to the active form1,25-dihydroxyvitaminD [1,25-(OH)2D], or calcitriol. This active form regulates the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins.

A drastic change in the plasma calcium concentration, either a decrease (hypocalcemia) or increase (hypercalcemia), is lethal; therefore, calcium level is tightly regulated by several hormones, which are three classical calcium-regulating hormones, namely parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], and calcitonin, as well as some other endocrine or paracrine factors [e.g., estrogen, prolactin, insulin-like growth factor-1, and fibroblast growth factor-23].

Pharmacodynamic Interactions
Calcium complexes tetracycline antibiotics rendering them inactive; the two drugs should not be given at the same time orally nor should they be mixed for parenteral administration.
The inotropic and toxic effects of cardiac glycosides and calcium are synergistic, and arrhythmia may occur if these drugs are given together (particularly when calcium is given i.v.)
Corticosteroids counteract the effects of cholecalciferol. Concurrent use of cholecalciferol and cardiac glycosides may result in cardiac arrhythmia. The possible interactions of calcium and cholecalciferol with other substances are all reflected in the SmPC for Calcium-D3. Some interactions of cholecalciferol, e.g. with heart glycosides, might be attributed to calcium rather than to cholecalciferol. As the present formulation is intended for oral administration and is aimed to replete deficient stores, e.g. due to insufficient sun exposure in combination with other risk factors, it can be assumed that the risk of severe systemic interactions is low if the product is taken as indicated.

IV.4 Clinical efficacy

The medical use of vitamin D/calcium supplementation is reflected by several published clinical studies. Particularly, the combination of 2,000 IU of vitamin D3 and 500 mg of calcium has been already investigated in a clinical study in Denmark published in 1984.Overall, vitamin D doses medically used as reflected in published clinical studies range from 400 IU/d up to > 10,000 IU/d and well-established use status of the combination under review can be reasonably concluded.

Calcium plus vitamin D in a daily dose of 500 mg calcium and 800-2000 IU vitamin D is effective for treatment of vitamin D and calcium deficiency in the elderly. Vitamin D and calcium supplement is also commonly used as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. This combination increases BMD and there is data that fracture prevention is achieved if used as an adjunct to specific osteoporosis treatment. Clinical data support a once daily dosing of calcium and vitamin D.

From a pharmacodynamic viewpoint it is reasonable to supplement a combination of cholecalciferol and calcium, as an adequate intestinal absorption of the latter depends on the presence of sufficient levels of the active vitamin D metabolite, 1,25(OD)2D3. The fixed combination of calcium and vitamin D in a single oral tablet represents a simplification of therapy (likely improvement in compliance, especially in elderly patients) and is plausible (concomitant deficiencies and calcium-sparing effect of vitamin D) and is therefore justified

according to the Note for guidance on fixed-combination medicinal products (CPMP/EWP/240/95).

IV.5 Clinical safety

Vitamin D and calcium are natural food components and have been administered as supplementation to natural intake for several decades. These medicinal substances are well known. Risk of intoxication is not foreseen for recommended daily doses of 500 mg calcium and 800 IU vitamin D in the proposed indications. Once daily dosing is accepted.
The chewable tablet 500mg / 2000 IU has a higher vitamin D content than previously approved combination products with these substances. However, as a monoproduct, the strength 2000 IU/day of vitamin D is approved for treatment of vitamin D deficiency. This strength is also lower than the upper limit of vitamin D for adults set by EFSA, 4,000 IU/day. The dose of vitamin D needed is dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D) and the severity of the disease. The vitamin D dose should also be adjusted according to the patient´s response to treatment as there may be long-term safety risks associated with vitamin levels above the normal range.

IV.6 Risk Management Plans

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 Bencium 500mg / 2000 IU chewable tablets and Bencium 500mg / 800 IU chewable tablets.

Safety specification

Summary of safety concerns	
Important identified risks	• Hypercalcemia • Nephrolithiasis • Nephrocalcinosis
Missing information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet 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

Calcium and colecalciferol (vitamin D3) are both physiological agents which are essential for bone mineralisation. A sufficient dietary intake of calcium and adequate concentrations of vitamin D are needed to prevent bone mineral release. If calcium and vitamin D levels fall below the physiological requirements and international recommendations, a supplementation of calcium and vitamin D to vitamin D deficient subjects, is recommended by expert consensus. Risk of intoxication is considered low for recommended doses in proposed indications.

The quality of Bencium is found adequate. There are no objections to approval of Bencium, from a non-clinical and clinical point of view. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bencium (CalciBen), Chewable tablet, 500mg / 800 IU and 500mg / 2000 IU, was positively finalised on 2018-12-11.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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