LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Calcomben
(cholecalciferol, calcium carbonate)

SE/H/2549/01-03/DC

This module reflects the scientific discussion for the approval of Calcomben. The procedure was finalised at 2026-04-16. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Calcomben, 500 mg/400 IE, 500 mg/800 IE, 1000 mg/800 IE, Chewable tablet.

The active substance is cholecalciferol, calcium carbonate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

The intake of both calcium and vitamin D in the diet declines with age. Low calcium intake in combination with hypovitaminosis D compromises intestinal calcium absorption, resulting in secondary hyperparathyroidism, accelerated bone loss, aggravation of existing osteoporosis and increased risk for fractures. Therefore, a supplement with calcium and vitamin D is important in the prevention of age-related bone loss and osteoporosis.

II.2 About the product

Calcomben contain the active ingredients calcium and cholecalciferol (Vit D). It is intended for prevention and treatment of calcium and vitamin D deficiency in elderly people, and as a supplement in addition to specific osteoporosis treatment of patients at risk of calcium and vitamin D deficiency.
The proposed doses are:
500 mg/400 IU chewable tablet: 2 tablets daily
500 mg/800 IU chewable tablet: 1 tablet daily
1000 mg/800 IU chewable tablet: 1 tablet daily

II.3 General comments on the submitted dossier

The application for Calcomben, 500 mg/400 IE, 500 mg/800 IE, 1000 mg/800 IE, Chewable tablet, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member state (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP

Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
N/A for this literature-based application.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of calcium carbonate and cholecalciferol are well known. As calcium carbonate and cholecalciferol is a widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is thus appropriate.

Environmental Risk Assessment (ERA)
Since Calcomben is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, calcium carbonate and cholecalciferol are not expected to pose a risk to the environment.

There are no objections to approval of Calcomben from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial, a bridge must be established between the formulations used in studies to support efficacy/safety and the applied for formulation. The Applicant has provided a relevant discussion of the issue, comparing their formulation to other approved formulations and discussed relevant clinical aspects. In addition, in vitro dissolution data has been provided which is assessed in the quality section. The product will be taken as a complement to dietary calcium and vitamin D3, which might be highly variable, and the patient response to treatment should be monitored. 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. The intent of supplementation treatment is to increase the body deposit of calcium and D3 on a long-term basis. Moreover, as the plasma levels of calcium and vitamin D3 are 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. From a pharmacokinetic point of view, it is acceptable to use quality data to establish a bridge to the literature.

The pharmacokinetics of calcium and cholecalciferol has generally been sufficiently described and claims in the SmPC supported by adequate references.

Pharmacodynamics
No new data has been provided, only published literature data which is acceptable for these well-known substances. Vitamin D is required to maintain normal blood levels of calcium and phosphate, which in turn are needed for the normal mineralization of bone, as well as muscle contraction, nerve conduction, and general cellular function in all cells of the body.

Clinical efficacy
No new data has been provided, only published literature data which is acceptable for these well-known substances. Several studies support the benefit of an adequate intake of calcium and vitamin D for bone health. Vitamin D increases the availability of calcium and thus have a direct beneficial effect on bone mineralization. A number of clinical studies have shown beneficial effects of treatment with calcium plus vitamin D on bone mineral density (BMD) in elderly people. The Applicant has performed structured literature searches and discuss several studies showing elevation of vitamin D-levels and increases in bone parameters in the supplemented elderly populations, as well as a number of studies with increased favourable results of antiresorptive treatment for osteoporosis when combined with supplementation of vitamin D and calcium.
The efficacy of calcium and vitamin D3 is well known and have been appropriately addressed and supported by data in the clinical overview.

Clinical safety
No new data has been provided, only published literature data which is acceptable for these well-known substances.

The clinical safety of calcium and vitamin D is well-known and no new safety issues have been discovered in the overview. The Applicant has provided references and adequate justification for all safety statements put forward in the product information.

Pharmacovigilance system

Proposed MAH: EQL Pharma AB

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Calcomben.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan

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

Part V Risk minimisation measures

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

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.1 signed 13-Mar-2024 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

Vitamin D and calcium are essential nutrients, and a sufficient intake is needed to prevent bone mineral resorption. If calcium and vitamin D levels fall below the physiological requirements and international recommendations, a supplementation of calcium and vitamin D in deficient subjects, is recommended by expert consensus. An adequate intake of vitamin D and calcium is especially important to maximise benefit of antiresorptive treatment in osteoporosis patients. The risk of intoxication is considered low, and the clinical safety is well-known at recommended doses in the proposed indication. The benefit risk assessment is positive.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-