LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kalcium/Kolekalciferol Evolan, (calcium carbonate, cholecalciferol)

Asp no: 2020-0389, 2020-0388

This module reflects the scientific discussion for the approval of Kalcium/Kolekalciferol Evolan, Kalcium/Kolekalciferol Evolan Forte. The procedure was finalised on 2021-04-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for Kalcium/Kolekalciferol tablets contain 500 mg calcium and 10 or 20 µg cholecalciferol (corresponding to 400 or 800 IU vitamin D). The active substance is calcium carbonate, cholecalciferol (for prevention and treatment of vitamin D and calcium deficiency in the elderly and as vitamin D and calcium supplement, as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium 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 Substances

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

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

The drug substance specifications 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 Introduction

The non-clinical overview is based on published literature data only and no new data has been provided, which is acceptable for well-known substances.

III.2 Pharmacology

Cholecalciferol (vitamin D3) is a prohormone that is synthesized either from 7-dehydrocholesterol via UV irradiation or ingested via the diet. The most potent form of vitamin D3 is lα,25-

dihydroxycholecalciferol (calcitriol), a hormone which primary function is to regulate gene expression by its interaction with the nuclear vitamin D receptor, VDR, resulting in up- or down-regulation of gene expression. Calcitriol enhance the absorption of calcium and phosphor from small intestine and exert a major hormonal function by maintenance of physiological calcium and phosphor levels in blood as well as bone metabolism.

III.3 Toxicology

Repeat-dose dose toxicity

Vitamin D toxicity is associated with ectopic calcification, especially of the vascular wall. Calcitriol administered by oral intubation to rats and rabbits for 26 weeks, doses of 0.08 to 0.30 µg/kg/day resulted in calcifications in the renal tubules and cardiac myofibrils.

Genotoxicity

No signs of genotoxicity were detected.

Carcinogenicity

A 26-week study performed in rat was cited and showed that vitamin D stimulates chromaffin cell proliferation in rat adrenal medulla and development of phaeochromocytoma, a rare, benign tumour of the adrenal gland, resulting in elevated blood pressure, headache etc. The clinical relevance for this is unknown.

Reproductive and developmental toxicity

In rabbits, dosages of 0.3 µg/kg/day calcitriol produced signs of maternal toxicity and fetotoxic effects. Increased resorption rate and neonatal mortality were observed as well as multiple foetal abnormalities in two litters from a dose level of 0.3 µg/kg/day and 1 litter at 0.08 µg/kg/day. In rats, hypercalcemia was noted in pups from dams receiving calcitriol in a dosage of 0.08 and 0.3 µg/kg/day. No other abnormalities were found in the rat pups.

Moderately increased supplementation of calcium in rat was investigated with regard to the foetal development. Animals were administrated from 5 weeks prior mating up to Day 20 of gestation. No adverse findings were reported. In addition, a recent repeat dose oral toxicity/reproduction study of calcium carbonate provided a NOAEL of 1000 mg/kg bw/day, for developmental toxicity and authors conclude that there is no concern for reproductive effects of calcium carbonate at intakes below 1500 mg/kg bw/day.

III.4 Ecotoxicity/environmental risk assessment

The active substances are natural substances intended to substitute other products on the market, the use of which will not alter the concentration or distribution of the substances in the environment. Therefore, Kalcium-Kolekalciferol Evolan (Forte) is not expected to pose a risk to the environment.

III.5 Discussion on the non-clinical aspects

Kalcium/Kolekalciferol are well known substances and the clinical experience is well established. The literature data provided for the non-clinical assessment is sufficient and considered adequate.

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

No new pharmacokinetic data has been provided, 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.

The literature data provided for the assessment of pharmacokinetics is sufficient and considered adequate.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new data has been provided, only published literature data which is acceptable for these well known substances. The efficacy of calcium and vitamin D3 is well known and has been adequately addressed in the clinical overview.

In the clinical studies referred to in the overview it was shown that the combined use of vitamin D and calcium resulted in a small reduction in hip fracture risk and also a reduction in risk for other fractures.

Supplementation with vitamin D3 alone or calcium alone has not been shown to reduce fracture rate.

IV.5 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 most common clinical adverse effects are all due to hypercalcemia.

IV.6 Risk Management Plans

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 Kalcium/Kolekalciferol Evolan, 500 mg/800 IE, 500 mg/400 IE, Film-coated tablet

Safety specification

Table: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance Plan

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

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

Summary of the RMP

The submitted Risk Management Plan, version 0.1 signed 17 January 2020 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 MPA;
- 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.

IV.7 Discussion on the clinical aspects

Calcium carbonate and cholecalciferol are well known substances. 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.
The literature data provided in this application support their efficacy and did not show any new safety issues.

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 PIL 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

Both the benefits and risks of Vitamin D and Calcium are well known and have been supported in this application by bibliographic data. The benefit/risk balance is considered positive.

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

Kalcium/Kolekalciferol tablets contain 500 mg calcium and 10 or 20 µg cholecalciferol (corresponding to 400 or 800 IU vitamin D) was approved in the national procedure on 2021-04-19.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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