LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kalcium/Kolekalciferol Evolan Citron, Kalcium/Kolekalciferol Evolan Spearmint (cholecalciferol, calcium)

Asp no: 2021-0169, 2021-0171, 2021-0170

This module reflects the scientific discussion for the approval of Kalcium/Kolekalciferol Citron Evolan, Kalcium/Kolekalciferol Spearmint Evolan. The procedure was finalised on 2022-01-28. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Kalcium/Kolekalciferol Citron Evolan, Kalcium/Kolekalciferol Spearmint Evolan, 500 mg/400 IE, 500 mg/800 IE, Chewable tablet.

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

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

The application for Kalcium/Kolekalciferol Evolan Citron, Kalcium/Kolekalciferol Evolan Spearmint, Chewable tablet 500 mg/800 IE, 500 mg/400 IE, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

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.

Calcium is an endogenously occurring element, absorbed from intestine actively and by passive diffusion. The active transport is dependent on vitamin D. In addition, other factors such as pH, age and oestrogen status affect absorption of calcium.

The pharmacology of calcium/cholecalciferol is well-known. Secondary pharmacology, safety pharmacology and pharmacodynamic drug interactions have not been discussed by applicant. This is considered acceptable for this well-established use product based on the long clinical experience of similar products.

Pharmacokinetics

Absorption

Cholecalciferol (vitamin D3) is either synthesized in the skin from 7-dehydrocholesterol via UV irradiation or absorbed through the small intestine from diet.

18–40% of the dietary calcium is absorbed from intestine by both passive diffusion and active transport by the calcium binding protein, calbindin. When the requirement of calcium is increased, the absorptive capacity of the gut is increased, and the renal excretion is regulated. Active absorption of Ca is highly dependent on vitamin D, and deficiency of vitamin D decreases the absorption of Ca.

Metabolism

Cholecalciferol is transported to the liver by vitamin D plasma protein (VDP), hydroxylated to 25-hydroxycholecalciferol (calcidiol). Calcidiol is further hydroxylated to 1α, 25Dihydroxycholecalciferol (calcitriol). This is the most active metabolite of cholecalciferol and regulates intracellular and extracellular concentrations of calcium in order to maintain a physiological range. Intracellular vitamin D receptors (VDR) with ligand selectivity for calcitriol are found in nearly all vertebrates, including mammals (human, mouse).

The majority of absorbed calcium is stored in the skeleton. Calcium absorbed from the diet is excreted in the urine and unabsorbed calcium in faeces. Renal excretion by glomerular filtration is reabsorbed in renal tubule by 98%. This process is regulated by active vitamin D and parathyroid hormone (PTH). Excess carbonate is excreted as CO2 via respiration.

Toxicology

Single and Repeat-dose dose toxicity

Applicant has presented results from oral LD50 studies for vitamin D in mice, rat and dog. Oral LD50 for mice was 23.7 mg/kg and 10 mg/kg for rats. Acute lethal dose for dogs was 13 mg/kg.

Vitamin D toxicity is associated with ectopic calcification, especially of the vascular wall. Repeated toxicological studies in rats and rabbits for 26 weeks, at doses of 0.08 to 0.30 µg/kg/day resulted in calcifications in the renal tubules and cardiac myofibrils. In addition, genetically modified mice, such as FGF23−/−and Klotho−/−mice exhibiting an altered mineral homeostasis due to a high vitamin D activity showed features of premature aging including ectopic calcification.

Nephrocalcinosis has been reported in a rat study, which was not considered relevant to human since rat is more prone to develop mineralization of the renal tubule epithelium due to diet than human. Nephrocalcinosis was not found in a 91-day toxicity study in Beagle dogs, receiving equivalent calcium levels as the rats. Nephrocalcinosis was not found in a study performed in Wistar rats, however, haematological and biochemical effects were reported but considered non-adverse and agreed with the no adverse event level (NOAEL) of 1000 mg/kg bw/day identified, which was the highest dose tested.

Genotoxicity
In vitro tests and In Vivo tests of genotoxicity was tested for vitamin D2 and D3. No signs of genotoxicity were detected.

Carcinogenicity
The available data for assessing the carcinogenic potential of vitamin D is very limited. A 26-week study performed in rat has been cited and shows 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 and headache.

Reproductive and developmental toxicity
In rabbits, dosages of 0.3 µg/kg/day calcitriol produced signs of maternal toxicity and fetotoxic effects. When pregnant rabbits treated with vitamin D3, 0.3 µg/kg/day from Days 7 through 18 of gestation, 3/16 rabbits died. In addition, maternal weight loss, 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 and hypophosphatemia were noted in pregnant female rats treated with 0.08 and 0.3 µg/kg/day, as well as increased serum urea nitrogen at 0.3 µg/kg/day. 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.
Based on the long clinical experience on the use of vitamin D supplementation, this is considered acceptable.

Environmental Risk Assessment (ERA)

The active substance are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Calcium/Cholecalciferol is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
In a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. 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. The intent of supplementation treatment is to increase the body deposit of calcium and vitamin D3 on a long-term basis. 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 bridge to the literature is considered sufficient.

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.

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 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.

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.

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 Kalcium/Kolekalciferol Evolan Citron and Kalcium/Kolekalciferol Evolan Spearmint.

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 Dec 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Kalcium/Kolekalciferol Evolan 500 mg/800 IE film-coated tablets, Asp no: 2020-0389. The bridging report submitted by the applicant has been found acceptable.

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 of this product is positive.

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

N/A

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

N/A

VII. APPROVAL

Kalcium/Kolekalciferol Citron Evolan, Kalcium/Kolekalciferol Spearmint Evolan, 500 mg/400 IE, 500 mg/800 IE, Chewable tablet was approved in the national procedure on 2022-01-28.

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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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