LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kolekalciferol Evolan
cholecalciferol

This module reflects the scientific discussion for the approval of Kolekalciferol Evolan. The procedure was finalised on 2021-06-29. 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 Kolekalciferol Evolan, 2000 IE, 800 IE, Tablet.

The active substance is kolekalciferol. 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.

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. Cholecalciferol is converted to 25-hydroxycholecalciferol in the liver and further metabolized in the kidney mitochondria to its biological active forms, 24,25- or lα,25-dihydroxycholecalciferol. The most potent form of vitamin D3 is lα,25-dihydroxycholecalciferol (calcitriol). Calcitriol is 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.

Calcitriol and its analogues have been shown to be active in VDR null mice suggesting other receptors responding to non-physiological levels of vitamin D compounds. Studies in VDR-ablated mice have also confirmed that the most critical role of Calcitriol is the activation of genes controlling intestinal calcium transport. Studies on neonatal mice have shown that vitamin D deficiency results in epigenetic changes in invariant natural killer T-cells (iNKT cells) that cannot be rescued by later exposure to vitamin D or 1,25D3, resulting in a reduction in the number of iNKT cells (Yu S et al., 2011).

Vitamin D compounds are to a large extent bound to vitamin D plasma proteins (VDP) and with a lesser affinity to albumin and lipoproteins.

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.

The estimated Tmax following a single oral dose (70,000 IU) of cholecalciferol to pregnant and non-pregnant women is 11 days, based on 25-hydroxycholecalciferol. Approximately 30% of the AUC occurred post-28 days.

Metabolism

25-OH-cholecalciferol–24-hydroxylase (24-OH-ase) in the kidney mitochondria, hydroxylates 25-hydroxycholecalciferol to 24, 25-dihydroxycholecalciferol. It has been suggested that the 24-hydroxylation is the initial step in the degradation process. The final degradation product of cholecalciferol is calcitroic acid, which is excreted in urine.

Vitamin D binding protein (VDP) is cleared from plasma with a half-life of 1.7 days, which is shorter than the 5-day half-life of albumin. Within 1 hour after injection of radiolabelled VDP, the radiolabel is present in a greater concentration than in plasma within the following tissues: kidney, liver, skeletal muscle, heart, lung, intestine, testis, and bone. In contrast to VDP, its ligand, 25(OH)D, is cleared slowly from the body, with a half-life of about 10 days in both rabbit and human. The binding of 25(OH)D to VDP does not affect the turnover or the tissue uptake of VDP.

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Toxicology

Single and Repeat-dose dose toxicity

Applicant has presented results from oral LD50 studies for vitamin D in rat and dog.
Vitamin D toxicity is associated with ectopic calcification, especially of the vascular wall. This has been observed in rodents and patients exposed to high doses of exogenous vitamin D, as well as in mice.

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.

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.
Based on the long clinical experience on the use of vitamin D supplementation, this is considered acceptable.

Environmental Risk Assessment (ERA)

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, Kolekalciferol is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
The assessment of the clinical pharmacokinetics of vitamin D3 is based on the information and references presented in the submitted updated Clinical Overview as of March 2021. The proposed Kolecalciferol Evolan 800 IU and 2000 IU tablets are intended for oral use.

There is no pharmacokinetic data specific for the currently applied product, which is acceptable. Due to the nature of the active substance, it is not considered necessary to compare the bioavailability of vitamin D from the new product with that from existing vitamin D containing products on the market. The product is intended to be a complement to dietary 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 vitamin D3 is controlled by a number of physiological processes and factors, the true absorption of this partly endogenous substance may be difficult to determine in a bioavailability study.

The products subject to this application according to Article 10a, WEU, contains same amount of active substance and similar excipients as the products marketed in Sweden which is supportive.

The revised Clinical Overview provided by the Applicant is found acceptable and the references given are considered to justify the PK characterisation and to support the claims in the proposed SmPC.

Pharmacodynamics
The applicant has presented a number of publications detailing the mode of action and dose/effect relationship for cholecalciferol. As these particulars are well known from various approvals of medicines, they are not presented in detail here. Most of the references presented concerns doses, dose frequencies and dose durations that are not relevant for the current application. Overall, it can be concluded that daily treatment with 800 IE or 2000 IE dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment is appropriate. The daily dose should not exceed 4000 IU.

Clinical efficacy
This WEU-application for cholecalciferol aims at documenting one indication for the higher strength (2000 IU) i.e. *prevention and treatment in case of measured serum levels lower than < 25 nmol/l in adults and adolescents*. This indication is also suggested for the lower strength (800 IU) in addition to a second indication i.e. *complementary to specific treatment of osteoporosis in combination with calcium*. Both these indications are regarded as well established in EU and thus the legal base for the application is valid.

The applicant's expert refers to numerous publications, including metanalyses and reviews. Various doses and dosing frequencies are studied and the efficacy levels recorded varies with study design and population studied. Overall, it can be concluded that there is support for the suggested indications with the posologies proposed i.e. 800-4000 IU daily dependent on need.

Clinical safety
The applicant's expert has summarised data on safety for cholecalciferol focussing primarily on doses higher than the proposed, especially bolus doses given monthly. The data provided is nevertheless deemed sufficient to justify the upper dose limit of 4000 IU daily.

In the SmPC the following adverse reactions are listed:

- Hypersensitivity reactions including angioedema (frequency: not known).
- Hypercalcemia (frequency: uncommon)
- Hypercalciuria (frequency: uncommon)
- Pruritus, rash and urticaria (frequency: rare)

There is scarce data provided to justify this listing. Nevertheless, as hypersensitivity reaction (including skin reactions) are well known and presented in various SmPC for Vitamin D products this inclusion is appropriate and on request the applicant completed their presentation with appropriate data. With regard to hypercalcemia/hypercalciuria there is an apparent discrepancy between the listing and the applicant's presentation of data as the latter is focus on overdoses and certain contraindicated conditions only. In response to the LoQ the applicant provided justification for retaining these two items.

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 Cholecalciferol Evolan.

Safety specification

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.

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 submitted Risk Management Plan, version 0.1 signed 12-Aug-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

The user test of the Kalcium/Kolekalciferol Evolan leaflet was assessed and accepted in dnr 5.4.1-2020-31914.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefits and risks of Vitamin D 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/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

Kolekalciferol Evolan, 2000 IE, 800 IE, Tablet was approved in the national procedure on 2021-06-29.

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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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