LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kolekalciferol Evolan
(Cholecalciferol)

Asp no: 2017-1002

This module reflects the scientific discussion for the approval of Kolekalciferol Evolan. The procedure was finalised on 2018-07-06. 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 Kolekalciferol Evolan, oral drops, solution; 800 IU/drop. The active substance is cholecalciferol (Vitamin D and analogues).

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

Pharmacodynamic, pharmacokinetic and toxicological properties of vitamin D are well-known and text-book knowledge. Products containing 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. No further nonclinical studies are required and the applicant provides none.

Ecotoxicity/environmental risk assessment
An ERA is not required for vitamins 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

Vitamin D deficiency can cause rachitis in children, osteomalacia in adults and contributes, with other factors, to osteoporosis in the elderly.
Optimal management of vitamin D deficiency is dependent on its underlying cause and treatment must be individualized with regard to pathogenesis and severity of the disorder.

IV.2 Pharmacokinetics

No pharmacokinetic studies have been performed with the product. For pharmacokinetic properties of vitamin D3, the applicant refers to literature data. The clinical overview was compiled by Georgi Tsvetanov Momekov, MSc (Pharm.), PhD, Assistant professor, Dept. "Pharmacology, pharmacotherapy & toxicology", Faculty of Pharmacy, Medical University-Sofia, 2 Dunav Stt., 1000, Sofia, Bulgaria. It is dated July 2017 refers 73 publications up to 2017. The presented bibliography is deemed acceptable regarding pharmacokinetics.

In summary, concerning PK properties, absolute bioavailability data for cholecalciferol is unavailable. However, the vitamin appears to be well-absorbed after oral doses. Cholecalciferol is absorbed from the small intestine and bile is essential for the absorption process (primarily deoxycholic acid). There appear to be no clinically relevant interaction with food. Cholecalciferol is transported to and stored in liver, adipose, and muscle tissue. Cholecalciferol is inactive until metabolic conversion. It is first hydroxylated in the liver via vitamin D 25-hydroxylase to 25-hydroxycholecalciferol (calcifediol); subsequent metabolism of calcifediol occurs in the kidney. The elimination half life is 19 to 48 hours, which represents initial plasma half-life; however, storage and slow release from tissues occurs, and the terminal half-life may exceed 3 weeks.

Regarding the bridge between the formulation applied for and formulations used in the bibliography, no concerns are raised. The objective of the pharmaceutical development programme was to obtain formulation containing cholecalciferol in the same pharmaceutical form and strength and route of administration as already marketed product Vigantol oil 0.5 mg/ml oral drops. The formulations used in the bibliography underlying "efficacy and safety aspects" in this application are however numerous but this is not considered to be an issue given that it has previously been reported that serum 25(OH)D levels following cholecalciferol administration with dosage forms such as oil, pills/tablets, capsules, solution, fortified rye bread, dissolved in ethanol, drops, or as lactose microencapsulated, etc, were efficient in increasing 25(OH)D levels independent of the pharmaceutical form.

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been conducted and none are needed for this WEU application.

Itself cholecalciferol exhibit little in the way of biologic activity. It undergoes hydroxylation in the liver to form 25-hydroxyvitamin D by action of the enzyme vitamin D-25 hydroxylase. 25-Hydroxyvitamin D serves as the primary storage form of vitamin D hormone. To become biologically active, 25-hydroxyvitamin D requires further hydroxylation to form the active calcium and phosphorus-regulating hormone 1,25-dihydroxyvitamin D by action of the enzyme 25-hydroxyvitamin D-1a-hydroxylase. This hydroxylation step takes place primarily in the kidney and is tightly regulated by circulating PTH, phosphate, and calcium levels. Thus, vitamin D deficiency can result from nutritional deprivation, inadequate sunlight exposure, impaired gastrointestinal absorption, reduced synthesis of 25-hydroxyvitamin D and/or 1,25-dihydroxyvitamin D or end-organ resistance to 1,25-dihydroxyvitamin D. The characteristic skeletal disturbance in vitamin D-deficient states is osteomalacia and rickets in children [Elder CJ and NJ Bishop 2014, Orwoll ES 2003, Wharton B and N Bishop 2003].
Vitamin D status and hence the efficacy of cholecalciferol treatment is currently best assessed by measurement of serum 25(OH)D [Holick MF et al. 2011]. As there is a broad inverse relationship between serum 25(OH)D and parathyroid hormone (PTH), the threshold serum 25(OH)D concentration below which PTH increases above the normal range has been used to define biochemical criteria for vitamin D insufficiency. However, the inverse relationship between serum 25(OH)D and PTH may be influenced by age, calcium intake, physical inactivity, renal function, ethnicity, magnesium status and vitamin D binding protein. Furthermore, the use of different assays for 25(OH)D and PTH may also influence the apparent threshold 25(OH)D concentration at which secondary hyperparathyroidism occurs. As a result, there is no clear consensus on the biochemical criteria that define vitamin D deficiency and insufficiency [Francis R et al. 2013, Holick MF et al. 2011]. In Sweden, vitamin D deficiency requiring treatment is commonly defined as serum 25(OH)D concentration <25 nmol/l.

IV.4 Clinical efficacy

Vitamin D deficiency results in inadequate absorption of Ca2+ and phosphate. The consequent decrease of plasma Ca2+ concentration stimulates PTH secretion, which acts to restore plasma Ca2+ at the expense of bone. Plasma concentrations of phosphate remain subnormal because of the phosphaturic effect of increased circulating PTH. In children, the result is a failure to mineralize newly formed bone and cartilage matrix, causing the defect in growth known as rickets. As a consequence of inadequate calcification, bones of individuals with rickets are soft, and the stress of weight bearing gives rise to bowing of the long bones.
In adults, vitamin D deficiency results in osteomalacia, a disease characterized by generalized accumulation of undermineralized bone matrix. Vitamin D has numerous functions within the body, but evidence between supplementation and health benefit beyond bone health are lacking despite a large number of observational studies and meta-analyses.

Rickets is characterised by a triad of clinical symptoms: skeletal changes (with deformities, craniotabes, and growth retardation), radiologic changes (widening of the metaphyseal plates, decreased mineralisation, deformities) and increases in bone alkaline phosphatase (ALP) activity in serum (Wharton and Bishop, 2003). Depending on the severity and duration of vitamin D deficiency, initial hypocalcaemia progresses to normocalcaemia and hypophosphatemia, because of increased PTH secretion and, finally to combined hypocalcaemia and hypophosphatemia when calcium can no longer be released from bone. Osteomalacia is characterised by increased bone resorption and suppression of new bone

mineralisation (Lips, 2006), and serum calcium concentration is often normal (2.25–2.6 mmol/L) despite the undermineralisation of bone. The clinical symptoms of vitamin D deficiency in adults are less pronounced than in children, and may include diffuse pain in muscles and bone and specific fractures. Muscle pain and weakness (myopathy) that accompany the skeletal symptoms in older adults may contribute to poor physical performance, increased risk of falls/falling and a higher risk of bone fractures.

Effect of Vitamin D supplementation on absolute change in 25(OH)D concentrations

An exhaustive systematic review of Cranney commissioned by the Institute of Medicine (IOM) has analyzed a total of 74 RCTs in 81 published reports that evaluated the effect of vitamin D supplementation on circulating 25(OH)D concentrations [Cranney A et al. 2007]. Seven trials included infants, but few of these studies used vitamin D3. One trial suggested that 200 IU of vitamin D2 may not be enough to prevent vitamin D deficiency, in some infants residing at northern latitudes. A dose-response was noted in this same trial (100, 200, 400 IU/day). Consistent responses to vitamin D supplementation were noted across the seven trials, and some trials suggested that infants who are vitamin D deficient, may respond differently and require higher doses of vitamin D [Cranney A et al. 2007].

There were four trials that examined the effect of vitamin D on 25(OH)D in children or adolescents with doses ranging from 200 to 2,000 IU of vitamin D3/ day and 400 IU of vitamin D2. In these investigations there were consistent increases in 25(OH)D concentrations ranging from 8 nmol/L (200 IU), 16.5 (with 600 IU D3) to 60 nmol/L (2,000 IU of vitamin D3) [Cranney A et al. 2007].

The systematic review identified and analyzed six small trials of vitamin D supplementation in pregnant or lactating women. No randomized trials studied the effect of 400 IU vitamin D3. Three trials used 1,000 IU of vitamin D2 and one trial used 1,000 IU of vitamin D3. Treatment with 1,000-3,600 IU/day of vitamin D2 and 1,000 IU/day of vitamin D3 resulted in significant increases in serum 25(OH)D concentrations in lactating mothers and in cord blood. One trial found that supplementation of lactating mothers with 1,000 IU of vitamin D2 during winter months did not increase serum 25(OH)D concentrations in the infants [Cranney A et al. 2007].

Ten small trials included premenopausal women and younger males. Three trials compared vitamin D2 to vitamin D3 in healthy young adults. Of these, one trial analyzed content of the tablets. Doses of vitamin D3 ranged from 600 to 10,000 IU/day and vitamin D2 (4,000 IU/day or 50,000 to 100,000 for one dose). Three trials found that vitamin D2 and D3 in healthy adults may have different effects on serum 25(OH)D concentrations. Vitamin D2 appeared to have a smaller effect on serum 25(OH)D, which may have been due to more rapid clearance and/or different metabolism than vitamin D3. One trial compared 100,000 IU vitamin D2 orally versus injection and found a greater variability in response with the intramuscular preparation. A dose-response effect was noted in those trials that used multiple doses of vitamin D3 [Cranney A et al. 2007].

This systematic review also analyzed 44 trials that were conducted exclusively in postmenopausal women and older men, with 14 of these in elderly populations living in long-term care or nursing homes. One trial was in early postmenopausal women. Doses of vitamin D3ranged from 100 to 4000 IU/day and 9,000 IU vitamin D. One trial was conducted in African American women. One trial found that wintertime declines in serum 25(OH)D were prevented with 500 IU of vitamin D3daily. A dose response with increasing doses of vitamin D3 was noted although there was a variability in response to similar doses across trials that may have been due to differences in serum 25(OH)D assays or baseline 25(OH)D status. Although some trials suggested a greater response to vitamin D in populations that were vitamin D deficient at baseline compared to those who were not, this was difficult to assess due to heterogeneity of assays [Cranney A et al. 2007].

Of the total of 44 RCTs investigated the effect of oral vitamin D3 supplementation (± calcium) versus no treatment, placebo or calcium on serum 25(OH)D sixteen trials presented sufficient

data to combine results of the absolute change in serum 25(OH)D Concentrations and perform an meta-analysis. Combining the 16 trials with a random effects model demonstrated large heterogeneity of treatment effect, but nevertheless the point estimates for each trial consistently favored vitamin D3 treatment [Cranney A et al. 2007].

Prophylaxis of vitamin D deficiency in malabsorption
Intestinal malabsorption syndromes (e.g., short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, and malabsorptive bariatric surgery procedures) are all associated with impaired vitamin D absorption as a result of either rapid transit or enhanced fecal loss of 25-hydroxyvitamin D because of impaired enterohepatic circulation [Kennel KA et al. 2010]. Similarly, patients with chronic severe parenchymal and cholestatic liver disease frequently exhibit vitamin D deficiency resulting from the associated malabsorption syndrome combined with a decreased hepatic capacity to convert vitamin D to 25-hydroxyvitamin D [Orwoll ES 2003]. The applicant states that no randomized trials have been allocated in this patient group. It seems reasonable that the treatment should be individualized in malabsorption. Other forms of treatment than per oral supplementation should be considered in patients who do not respond to maximum recommended oral doses.

Most randomized, controlled studies of vitamin D supplementation have been focused on skeletal outcomes. As the majority of these studies involve the concomitant use of calcium supplements [Cranney A et al. 2007], it is not possible to distinguish those effects attributable specifically to vitamin D.
Maintenance supportive treatment in osteoporosis, in combination with calcium and with a specific anti-osteoporotic agent
Most randomized, controlled studies of vitamin D supplementation have been focused on skeletal outcomes. As the majority of these studies involve the concomitant use of calcium supplements [Cranney A et al. 2007], it is not possible to distinguish those effects attributable specifically to vitamin D. For supportive treatment in osteoporosis, daily doses approximately 400-1000 IU of vitamin D3 daily have been systematically investigated in clinical studies.

Prolonged vitamin D insufficiency may lead to low bone mineral density (BMD) and may dispose older subjects, particularly post-menopausal women, for osteoporosis, a situation characterized by a reduction in bone mass, reduced bone quality and an increased risk of bone fracture.
In spite of the uncertainty surrounding the subject of vitamin D with or without the addition of Ca
[MacLean et al. 2008], some general trends and results are apparent. Overall, the data supports the combined use of vitamin D and Ca for the treatment of osteoporosis. However, most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent [Boonen et al. 2006b]. Clinical trials with vitamin D and / or Ca to decrease fracture incidence generally have shown that trials with vitamin D and Ca had better results than vitamin D or Ca alone [Lips 2012].

Treatment secondary hyperparathyroidism
In secondary hyperparathyroidism, the conversion of 25-dihydroxy-vitamin D3 to 1,25-dihydroxy-vitamin D3 is usually reduced, and treatment with 25-dihydroxy-vitamin D3 in this condition is mainly indicated to ensure sufficient levels of the precursor. The indication “prevention and treatment of vitamin D deficiency” is therefore considered to cover this condition.

Comparison with other routes of application
While intramuscular administration results in 100% adherence, there are important factors to consider before usage, including an unpredictable bioavailability, slower onset of repletion and the additional administration burden in comparison to oral preparations. Parenteral vitamin D is therefore not the first-line recommendation within the current treatment guidances, primarily due to significant inter-individual variability in absorption [Francis R *et al.* 2013].

Dosage regimen
From the literature survey this overview is based on it is clear that that there is currently no established consensus on the dosing regimens of vitamin D [Anon. 2013, Francis R et al. 2013, Holick MF 2007, Holick MF et al. 2011, Hossein-nezhad A and MF Holick 2013, Vieth R 2001, Vieth R 2005].

For the indications of prevention of vitamin D deficiency and supportive treatment in osteoporosis, daily doses approximately 400-1000 IU of vitamin D3 daily have been systematically investigated in clinical studies. Similar doses are well established in prevention of vitamin D deficiency in adolescents and adults with an identified risk. Regarding children, the general recommendations vary between countries and organisations. The current prevention posology for patients at risk according to several organizations is around 400-500 IU. In the presence of cutaneous vitamin D synthesis, the requirement for dietary vitamin D is lower or may even be zero. Daily and weekly dosing of the same cumulative doses results in comparable 25(OH)D3 serum level.

Higher doses (up to corresponding doses of 4000 IU daily in adults and adolescents) may be necessary in the initial treatment of vitamin D deficiency, defined as serum 25-hydroxycalciferol (25OHD) <25 nmol/l. In these cases, the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. The maximum recommended daily doses should be in accordance with the current EFSA Tolerable Upper Intake Levels for adults, adolescents, children and infants.

Conclusions of efficacy
In conclusion, optimal management of vitamin D deficiency is dependent on its underlying cause and treatment must be individualized with regard to pathogenesis and severity of the disorder. Deficiency states associated with malabsorption may require pharmacological amounts of vitamin D. In most patients with vitamin D deficiency the object is to restore and maintain optimal serum 25(OH) vitamin D concentrations. Monitoring serum levels after vitamin D supplementation begins should provide an adequate guide for dose adjustments.

IV.5 Clinical safety

The following adverse events are mentioned in the SmPC for approved D-vitamin products (and proposed for Kolekalciferol Evolan): Hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea and hypersensitivity reactions such as pruritus, rash, urticaria.

Therapeutic doses of cholecalciferol are usually well tolerated, but aggressive dosing, especially in populations at risk (e.g. patients with sarcoidosis, and other chronic granulomatous conditions) poses risk of hypercalcemia and hypercalciuria. The toxic effects of vitamin D excess are primarily related to the role of free 1,25(OH)2D in the regulation of plasma calcium. Excessive production of 1,25(OH)2D or greatly increased plasma 25(OH)D

(which may displace 1,25(OH)2 D from DBP) may lead to elevated level of plasma calcium due partly to over stimulated intestinal absorption and partly to excessive calcium mobilization from bone. Hypercalcemia could also lead to an increased calcium excretion into urine, hypercalciuria. There is also limited evidence that high concentrations of vitamin D directly affect various organ systems such as kidney, bone, the central nervous system and the cardiovascular system.

The drug has few drug interactions, especially with drugs, which modulate serum calcium and can thus augment its effects or with drugs that cause fat malabsorption or induce microsomal enzymes.

Vitamin D administration is not contraindicated in patients with mild to moderate renal impairment, as long as adequate precautions are followed (Rodriguez-Martinez and Garcia-Cohen, 2002). However, severe kidney insufficiency, simultaneous administration of calcium is contraindicated.

Toxicity has been reported during vitamin D treatment of tuberculosis and in patients with active sarcoidosis (Sharma, 1996). Specialist advice should be sought before starting these patients in vitamin D therapy.

Following ingestion of e.g. 125–1 000 µg/day of vitamin D over a period of at least one month, the concentration of serum 25(OH)D increases, while that of 1,25(OH)2D is unchanged or even reduced (EFSA NDA Panel, 2012a; Jones, 2014). High serum 25(OH)D concentrations (> 220 nmol/L) may lead to hypercalcaemia, which may eventually lead to soft tissue calcification and resultant renal and cardiovascular damage (Vieth, 1999; Zittermann and Koerfer, 2008).

Studies that have shown a reverse-J-shaped curve for the relationship between mortality and 25(OH)D show a beneficial effect as 25(OH)D concentrations increase to 30 nmol/l, with lowest mortality at 50 nmol/l and then increased risk above 75 nmol/l.

In revising the Tolerable Upper Intake Levels (ULs) for vitamin D (EFSA NDA Panel, 2012a), data on possible associations between vitamin D intake or 25(OH)D concentration and adverse long-term health outcomes were considered. However, no studies reported on associations between vitamin D -intake and increased risk for adverse long-term health outcomes. Studies reporting on an association between 25(OH)D concentration and all-cause mortality or cancer were inconsistent. For adults, hypercalcaemia was selected as the indicator of hypervitaminosis D or vitamin D toxicity (EFSA NDA Panel, 2012a). Two studies in men supplemented with doses between 234 and 275 µg/day vitamin D3 showed no association with hypercalcaemia (Barger-Lux et al., 1998; Heaney et al., 2003a), and a No Observed Adverse Effect Level (NOAEL) of 250 µg/day was established 411 (Hathcock et al., 2007). Taking into account uncertainties associated with these two studies, the UL for adults was set at 100 µg/day.

In children, Scientific opinion on the tolerable upper intake level of vitamin D, EFSA Journal 2012;10(7):2813 states that considering phases of rapid bone formation and growth and the unlikelihood that adolescents have a lower tolerance for vitamin D compared to adults, the UL was set at 100 µg/day (corresponding 4000 IU= 8 drops of Kolekalciferol Evolan) for ages 11–17 years (EFSA NDA Panel, 2012a). The same consideration applied also to children aged 1–10 years, but taking into account their smaller body size, a UL of 50 µg/day (corresponding 2000 IU= 4 drops of Kolekalciferol Evolan) was selected (EFSA NDA Panel, 2012a).
For infants, data relating high vitamin D intakes to impaired growth and hypercalcaemia (Jeans and Stearns, 1938; Fomon et al., 1966; Ala-Houhala, 1985; Vervel et al., 1997; Hyppönen et

al., 2011) were used as indicators in the previous risk assessment by the SCF to set the UL at 25 µg/day (SCF, 2002a). The Panel retained the UL of 25µg/day (corresponding 1000 IU= 2 drops of Kolekalciferol Evolan) and noted that no long-term studies were available (EFSA NDA Panel, 2012a).
The Panel notes that two randomised controlled trials (RCTs) have been published after the assessment of the UL by the EFSA NDA Panel (2012a). In both RCTs, infants received vitamin D3 supplementation of 10, 30 or 40 µg/day, for a period of three months (Holmlund-Suila et al., 2012) or 12 months (Gallo et al., 2013), with concomitant increases in mean serum 25(OH)D concentrations. In the shorter term study (Holmlund-Suila et al., 2012), hypercalcaemia or hypercalciuria did not occur at any dose of vitamin D3 supplemented. In the longer term study (Gallo et al., 2013), the dose of 40 µg/day was discontinued prematurely because of elevated serum 25(OH)D concentrations above 250 nmol/L, a criterion a priori chosen by the authors to indicate hypervitaminosis D.

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 Kolekalciferol Evolan.

Safety specification

Summary of safety concerns	
Important identified risks	- Vitamin D overdose; - Hypercalcemia - Use in patients with renal impairment;
Important potential risks	- Concomitant use with cardiac glycosides;
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 now 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 Detremin 20 000 IE/ml oral drops, solution (SE/H/966/01/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Beneficial effects:
Clinical symptoms of vitamin D deficiency manifest as rickets in children and osteomalacia in adults. For the indications of prevention of vitamin D deficiency and supportive treatment in osteoporosis, daily doses approximately 400-1000 IU of vitamin D3 daily have been systematically investigated in clinical studies. Similar doses are well established in prevention of vitamin D deficiency in adolescents and adults with an identified risk. Regarding children, the general recommendations vary between countries and organisations. The current prevention posology for patients at risk according to several organizations is around 400-500 IU. In the presence of cutaneous vitamin D synthesis, the requirement for dietary vitamin D is lower or may even be zero.
Daily and weekly dosing of the same cumulative doses results in comparable 25(OH)D3 serum level.

Higher doses (up to corresponding doses of 4000 IU daily in adults and adolescents) may be necessary in the initial treatment of vitamin D deficiency, defined as serum 25-hydroxycalciferol (25OHD) <25 nmol/l. In these cases, the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. The maximum recommended daily doses should be in accordance with the current EFSA Tolerable Upper Intake Levels for adults, adolescents, children and infants.

Undesirable effects:
The following adverse events are mentioned in the SmPC for approved D-vitamin products: hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea, and hypersensitivity reactions such as pruritus, rash, urticaria.
Toxicity reported from vitamin D supplementation is rare. Toxicity manifests as hypercalcemia and
hypercalciuria, leading to renal failure as a results of nephrocalcinosis and nephrolithiasis and neurologic symptoms including coma. Excessive vitamin D intake is associated with additional adverse events, including pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting and weight loss.
These are all due to hypercalcaemia.
The data on associations between vitamin D intake and increased risk for adverse long-term health outcomes is scarce and inconsistent.

If higher than standard recommended doses are prescribed, monitoring and dose adjustments should be considered after the first month of treatment. The risk of medication errors leading to overdose is higher in infants and children compared to adults and adolescents.

Summary and Conclusion:
Well-established medicinal use of vitamin D for more than 10 years in the community is acknowledged and an application in accordance with Article 10a of Directive 2001/83/EC is valid. No new or additional studies have been conducted. The quality of Kolekalciferol Evolan is found adequate. The benefit/risk of the product 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

Kolekalciferol Evolan, 800 IU/drop, oral drops, solution, was approved in the national procedure on 2018-07-06.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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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