LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Calcium/Cholecalciferol Theramex (cholecalciferol, calcium carbonate)

SE/H/2512/001/DC

This module reflects the scientific discussion for the approval of Calcium/Cholecalciferol Theramex. The procedure was finalised on 2025-01-16. 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 Calcium/Cholecalciferol Theramex, 500 mg/1000 IU, Chewable tablet.

The active substance is cholecalciferol and calcium carbonate. 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 Calcium/Cholecalciferol Theramex, 500 mg/1000 IU, 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 PT and BE as concerned member states (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.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products

N/A

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/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 substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Calcium/Cholecalciferol Theramex contains a well-known medical substance, 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 Calcium 500 mg / Vitamin D_3 1000 IU, chewable tablets from a non-clinical point of view.

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 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 data was mainly based on quality aspects.

The pharmacokinetics of the active substances 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. The pharmacodynamics are sufficiently described by the Applicant.
The possible interactions of calcium and cholecalciferol with other substances are all reflected in the proposed SmPC.

Clinical efficacy
No new data has been provided, only published literature data which is acceptable for these well-known substances and this type of application.

Several studies support the benefit of an adequate intake of calcium for bone health. Vitamin D increases the availability of calcium, decreases the risk of hyperparathyroidism and may have a direct beneficial effect on bone. A number of clinical studies have shown beneficial effects of treatment with calcium plus vitamin D on bone mineral density (BMD) as well as on fracture rates in elderly people.

A vitamin D supplementation study from 1988 in institutionalised elderly in the Netherlands showed that a vitamin D supplement of 400 IU/day led to an increase in the mean serum 25(OH)D from 20 to 65 nmol/L and a supplement of 800 IU/day further increased mean serum 25(OH)D to 80 nmol/L (8803). Former European guidelines generally recommended a daily calcium intake of 700 - 800 mg for adults (≥ 800 mg daily for women aged 50 - 65 years), and a daily vitamin D intake of up to 400 IU for adults (400 IU daily for all adults aged 65 years and over). The DVO-guideline from 2009, recommends a total uptake of 1,000 mg/d calcium by adequate nutrition and a supplementation of 800 - 2,000 IU/d vitamin D, if adequate exposition to sunlight cannot be achieved.

A considerably lower intake is sufficient for individuals with regular effective sun exposure. However, many elderly patients are at high risk for vitamin D deficiency, including patients with malabsorption (e.g., celiac disease) and chronic renal insufficiency, housebound patients, chronically ill patients and others with limited sun exposure. The safe upper limit for vitamin D intake for the general adult population was set at 2,000 IU per day in 1997; recent evidence indicates that higher intakes are safe and that some elderly patients will need at least this amount to maintain optimal 25(OH)D levels. Intake may need to be adjusted upward to as much as 50 µg/day (2,000 IU/day) in individuals, who are obese, and in those with e.g. osteoporosis, limited sun exposure (institutionalised, homebound), and malabsorption, as well as in populations known to be at high risk for vitamin D deficiency, particularly in veiled women or darker-skinned individuals in northern countries. It is also suggested to elevate the vitamin D doses up to 4,000 IU/d for adults who are obese, have malabsorption or are on drugs known to interfere with the metabolism of vitamin D.

In 2011, the Endocrine Practice Guidelines Committee recommended that all adults aged 50 - 70 and 70+ years require at least 600 and 800 IU/d, respectively, of vitamin D to maximise bone health and muscle function. Among those age 65 and older a dose of 800 IU /d for the prevention of falls and fractures was recommended. However, to raise the blood level of 25(OH)D above 30 ng/mL may require at least 1,500 - 2,000 IU/d of supplemental vitamin D. This guideline is based on the recommendations made by the Institute of Medicine (IOM) for the Dietary Reference Intakes (DRI) for Calcium and Vitamin D in 2011, which was developed by a group of clinicians and scientists with expertise in vitamin D, metabolic bone disease and osteoporosis. New Recommended Dietary Allowances (RDA) for Vitamin D in normal subjects have been recently released by the IOM, on the basis of the work of experts who reviewed the available literature. For vitamin D, presuming minimal or no sun exposure, the RDA is suggested to be 600 IU/day for subjects aged 1 - 70 years and 800 IU/day for those older than 70. The target of therapy is to reach adequate levels of 25-hydroxyvitamin D, identified as 50 nmol/1 (or 20 ng/mL)

There is considerable disagreement on human calcium requirements, and this is reflected in the wide variation in estimates of daily calcium requirements made by different expert authorities. For example, expert committees in the US, UK and EU have established very different recommendations for calcium intake. Much of this divergence arises due to different interpretations of available human calcium balance data.

The recent DVO-guideline from 2014, recommends a total uptake of 1,000 mg/d calcium and a supplementation of 800 - 1,000 IU/d vitamin D, if adequate exposition to sunlight cannot be achieved. The total intake of calcium should not be higher than 2,000 mg/d (1401). The range from 400-800 mg/d points at the dietary requirements of healthy persons from 50 years on and implicate prevention, for women at increased risk should be given both calcium and vitamin D supplements. To achieve the greatest reduction in fracture risk, for them the dosage was recommended earlier in an order of 1,000 - 1,200 mg calcium (depending on baseline status) and 800 IU vitamin D daily). The average

consumption of calcium via diet and supplements was about 1,000 mg/d in the target population (51 - 80 years) in Germany in 2008.

Daily vitamin D dosages in clinical trials to prove fall prevention are reported up to 2,000 IU/d, but mostly 800 - 1,000 IU/d. RCTs to prove reduction of fractures with vitamin D in osteoporotic patients are available from less than 400 IU to doses of mostly 700 - 800 IU/d. A 2009 meta-analysis) on dose dependency of fracture prevention shows that anti-fracture efficacy in non-vertebral and hip fractures increased significantly with a higher dose of vitamin D and with higher achieved 25(OH)D blood levels, and fracture prevention could not be achieved with lower dosages of vitamin D (e.g. 400 IU). RCTs to prove non-vertebral fractures are also available with high bolus applications i.e. 100,000 IU D2 every 3 months.

The dose of vitamin D required to minimise bone loss was investigated in a double-blind, randomised 2-year study in 247 postmenopausal women receiving calcium citrate malate supplements of 0.5 g/d. Average dietary vitamin D consumption was 100 IU/d, which was then supplemented with either 100 IU/d or 700 IU/d to provide a total dose of either 200 IU/d or 800 IU/d. Over 2 years both treatment groups lost BMD from the femoral neck, but the patients given the higher dosage of vitamin D lost significantly less than those taking the lower dosage (-1.06 ± 0.34 vs. -2.54 ± 0.37, $p = 0.003$). Changes in spinal and whole-body bone densities did not differ by treatment group and were minimal after 2 years. Thus, 200 IU vitamin D/d is sufficient to limit bone loss from the spine and whole body in calcium supplemented postmenopausal women but is not adequate to minimise bone loss from the femoral neck of the hip. To prevent the latter a dose of 800 IU vitamin D daily appears to be required, and this dosage corresponds to current recommendations of organisations such as the WHO, ILAR, IFSSD and EFFO for treatment of osteoporosis up to 2003.

Overall conclusions on clinical efficacy

The medical use of vitamin D/calcium supplementation is reflected by several published clinical studies. Overall, vitamin D doses medically used as reflected in published clinical studies range from 400 IU/d up to > 10,000 IU/d and well-established use status of the combination under review can be reasonably concluded.

Calcium plus vitamin D in a daily dose of 500 mg calcium and 800-2000 IU vitamin D is effective for treatment and prevention of vitamin D and calcium deficiency in the elderly and other risk patients. Vitamin D and calcium supplement is also commonly used as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. This combination increases BMD and there is data that fracture prevention is achieved if used as an adjunct to specific osteoporosis treatment. Clinical data support a once daily dosing of calcium and vitamin D.

From a pharmacodynamic viewpoint it is reasonable to supplement a combination of cholecalciferol and calcium, as an adequate intestinal absorption of the latter depends on the presence of sufficient levels of the active vitamin D metabolite, 1,25(OD)2D3. The fixed combination of calcium and vitamin D in a single oral tablet represents a simplification of therapy (likely improvement in compliance, especially in elderly patients) and is plausible (concomitant deficiencies and calcium-sparing effect of vitamin D) and is therefore justified according to the Note for guidance on fixed-combination medicinal products (CPMP/EWP/240/95).

Many studies in the literature are performed with lower Vitamin D doses than for the product in this application. In addition, many approved products contain 500 mg Ca/400 IU cholecalciferol with a posology of 1-2 tablets per day. However, there are products with 500 mg Ca/2000 IU cholecalciferol approved and literature references have been provided to support the efficacy and safety for this combination.

The dose of vitamin D needed is dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D) and the severity of the disease, which could justify that a higher strength of vitamin D can sometimes be needed. The vitamin D dose should also be adjusted according to the patient´s response

to treatment as there may be long-term safety risks associated with vitamin levels above the normal range.
Even though most studies are performed in elderly risk factors for vitamin D deficiency (e.g. malabsorption, obesity and limited sun exposure) can also be present in adults. Therefore, the indication may include adults as well as elderly.

Vitamin D and calcium supplement is commonly used as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. This combination increases BMD and there is data that fracture prevention is achieved if used as an adjunct to specific osteoporosis treatment. The provided literature support this.

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

Calcium plus vitamin D is contraindicated in patients with hypercalcaemia, hypercalciuria, severe renal impairment, nephrolithiasis, hypervitaminosis D or hypersensitivity to any of the ingredients (calcium carbonate and cholecalciferol SmPC). Adverse reactions of a generally mild nature have been observed with calcium carbonate treatment, and include constipation, flatulence, nausea and diarrhoea. A possible effect of high calcium intake is that the absorption of other minerals, e. g. iron, may be reduced.

The main symptomatic effects of a calcium overdose are related to hypercalcaemia and include thirst, polyuria, anorexia, constipation, muscular weakness, fatigue and confusion. In severe cases nausea, vomiting and, rarely, cardiac arrythmias may occur. Serious adverse effects of calcium carbonate result from hypercalcaemia. A few such cases are reported in the literature, particularly in haemodialysis patients. Persistent high serum calcium levels may lead to irreversible renal damage and soft tissue calcification and extreme hypercalcaemia may result in coma and death.

Reports of severe hypercalcaemia during vitamin D/calcium treatment have occurred with doses of vitamin D exceeding 10,000 IU per day. Considering vitamin D, very large amounts over a long period can induce hypercalcaemia or toxic symptoms (more than 60,000 IU daily). In infants, vitamin D intoxication can occur after long-term doses of 2.5–5 times the recommended daily intake and cause hypercalcaemia, hypercalciuria and calcification of soft tissues.

The SmPC for calcium carbonate with cholecalciferol recommends that the product should not be used in patients with severe renal impairment (calcium carbonate and cholecalciferol SmPC). Calcium carbonate with cholecalciferol tablets should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be considered. In patients with severe renal insufficiency, vitamin D3 is not metabolised normally, and other forms of vitamin D should be used.

In a Cochrane meta-analysis, hypercalcaemia was reported more often when vitamin D or its analogues were given compared with placebo or calcium, a small increase in gastrointestinal symptoms were noted and a statistically significant increase in the incidence of renal calculi or renal insufficiency was also reported.
The safety of vitamin D and calcium supplement as an adjunct to osteoporosis treatment is well established. The vast majority of clinical studies have used dosages 400 IU or 800 IU of vitamin D.

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of vitamin D. For adults, hypercalcaemia was selected as the indicator of toxicity. Taking into account uncertainties associated with the clinical studies, the upper limit for adults including pregnant and lactating women was set at 4,000 IU/day.

Overall conclusions on clinical safety

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 of intoxication is not foreseen for recommended daily doses of 500 mg calcium and 1000 IU vitamin D in the proposed indications. Once daily dosing is accepted. The chewable tablet 500mg / 1000 IU has a higher vitamin D content than most of the previously approved combination products with these substances. This strength is lower than the upper limit of vitamin D for adults set by EFSA, 4,000 IU/day. The dose of vitamin D needed is dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D) and the severity of the disease. The vitamin D dose should also be adjusted according to the patient´s response to treatment as there may be long-term safety risks associated with vitamin levels above the normal range.

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 Calcium/Cholecalciferol Theramex.

Part II Safety specification

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 1.0 signed 11 Dec 2023 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.

V. USER CONSULTATION

The applicant has provided a commitment to submit results of user consultation for the package leaflet via a variation procedure within 3 months after completion of this decentralised procedure.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The medical use of vitamin D/calcium supplementation is reflected by several published clinical studies that are described in an adequate review. Overall, vitamin D doses medically used as reflected in published clinical studies range from 400 IU/d up to > 10,000 IU/d and well-established use status of the combination under review can be reasonably concluded.

Calcium plus vitamin D in a daily dose of 500 mg calcium and 800-2000 IU vitamin D is effective for treatment and prevention of vitamin D and calcium deficiency in the elderly and other risk patients. Vitamin D and calcium supplement is also commonly used as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. This combination increases BMD and there is data that fracture prevention is achieved if used as an adjunct to specific osteoporosis treatment. Clinical data support a once daily dosing of calcium and vitamin D.

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. The benefit-risk ratio is considered positive, and approval is recommended from the clinical point of view.

The quality of the generic product, Calcium/Cholecalciferol Theramex, is found adequate. There are no objections to approval of Calcium/Cholecalciferol Theramex, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

The decentralised procedure for Calcium/Cholecalciferol Theramex, 500 mg/1000 IU, Chewable tablet was positively finalised on 2025-01-16.

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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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