LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Calcium/Cholecalciferol Theramex (calcium carbonate, cholecalciferol)

SE/H/2261/01/DC

This module reflects the scientific discussion for the approval of Calcium/Cholecalciferol Theramex. The procedure was finalised on 2023-07-19. 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/2000 IE, chewable tablet.

The active substances are calcium carbonate and cholecalciferol (vitamin D3). 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/2000 IE, chewable tablet, is an application submitted according to Article 10a (WEU) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, ES, PT 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
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
Ca2+ is not only essential for bone mineralisation, but also for regulation of extracellular and intracellular processes. Ca2+ is the most abundant inorganic constituent of the bone, crucial for the maintenance of its physical strength.

Cholecalciferol (via 1,25-(OH)2D3) is a steroid that is involved in calcium homeostasis and acts via a receptor to increase the transcription of some mRNAs and inhibit the transcription of others. Receptors of 1,25-(OH)2D3 are found in many tissues, for example: the intestine, kidneys, bone, skin, lymphocytes, monocytes, and cardiac muscle, breast, and anterior pituitary gland. Moreover, vitamin D is required for bone development and maintenance.

Furthermore, vitamin D deficiency results in the poor intestinal absorption of Ca 2+ and often leads to hypocalcaemia. As a result of Ca 2+ deficiency, the protein of new bone fails to mineralise, although, in experimental animals, there is little evidence that vitamin D directly promotes mineralisation.

The Non-clinical Overview on the pre-clinical pharmacology considered adequate. Pharmacodynamic properties of calcium and cholecalciferol are very well-known and considered as text-book knowledge.

Pharmacokinetics
The absorption of Ca 2+ is mainly performed by a calcium-dependent ATPase active transport system located in epithelial cells. Passive diffusion also accounts for a smaller part of the absorption. Approximately 30 - 80% of the oral intake of Ca2 + is absorbed from the gastrointestinal tract, mainly from the upper small intestine. The skeleton contains 99% of total body calcium and the steady-state content of calcium reflects the net effect of bone resorption and bone formation. Although Ca2+ are absorbed, distributed, and excreted, there is no metabolism in the strict sense. Calcium is excreted in the faeces (unabsorbed calcium) via bile and pancreatic juice into the lumen of the GI tract. Although being filtered by the kidney, 98-99 % of the calcium is reabsorbed. Some other pharmaceuticals affect Ca2+ concentrations, e.g., tetracyclines, thiazide diuretics, corticosteroids. These interactions (amongst others) are integrated in the SmPC.

The normal plasma concentrations of cholecalciferol are within the range of 10 - 80 ng/ml, and peak concentrations are achieved about 4 h after oral administration. Vitamin D3 is transported in plasma bound to globulin vitamin D binding protein which maintain stable serum stores of vitamin D metabolites to stabilise and maintain serum levels of vitamin D against variable vitamin D availability. In the liver cholecalciferol is converted to 25-(OH)D3 which is subsequently converted in the proximal tubules of the kidneys to 1,25-(OH)2D3. 25-hydroxylated metabolites are stored in fat and muscles for prolonged periods, and the vitamins may be distributed in milk, although at reduced concentrations. Vitamin D metabolites are excreted mainly in bile and faeces. The liver converts vitamin D to 25OHD. The kidney converts 25OHD to 1,25(OH)2D and 24,25(OH)2D. Other tissues contain these enzymes, but the liver is the main source for 25-hydroxylation, and the kidney is the main source for 1α-hydroxylation. Pentobarbital use in rats have been shown to significantly reduce concentrations of 1,25- (OH)2D3. Furthermore, concomitant use of glucocorticoids has been shown to reduce the efficacy of vitamin D.
In rats, it has been shown that diabetes mellitus type II, insulin resistance or renal injury is associated with decreased formation of active vitamin D, possibly due to decreased activity of 1-α-hydroxylase.

Medicinal products containing calcium and vitamin D have been available in Europe for decades and their use is well-established with recognised efficacy and acceptable safety. The daily dose levels proposed for the product are within the dosage range used in current clinical practice.

Toxicology

General toxicity

-*Calcium*

High variability is a direct consequence to certain salts, e.g.: arsenate form. For calcium carbonate, the LD50 in rats = 6,450 mg/kg b.w. which this is approximately 650-fold higher than the recommended daily maximum dose of 10 mg/kg b.w. for a 50 kg patient. It is thus agreed that the calcium component of Calcium-D3 tablets is not considered to have any potential for single dose toxicity when used according to the restrictions specified in the SmPC.

Preclinical data on repeated-dose toxicity in animals was not provided/found by the applicant. Instead, clinical data is presented. The toxic symptoms relate to long-term use, often seen during treatment of a chronic disease. The various toxic symptoms of calcium salts are usually explained by the effects of elevated Ca2+ concentrations. Different forms of hypercalcaemia can have both cardiovascular, neurological and gastrointestinal toxic effects. The acid-base or fluid-electrolyte balance may also be impaired.

-*Vitamin D*

Cholecalciferol LD50 for dogs (p.o.), rats (p.o.) and mice (i.p.) are 13, 42 and 136 mg/kg, respectively, according to the provided literature. Since the daily intake of cholecalciferol (as specified in the SmPC) is 50 µg cholecalciferol per day, a 50 kg human this dose correspond to 1.0 µg/kg b.w. (or 40 IU/kg b.w. cholecalciferol). Therefore, the clinical dose is approximately 13000-fold and 42,000-fold lower than a representative preclinical LD50 value following p.o. administrations of cholecalciferol for dogs and rats, respectively. Thus, the vitamin D component of Calcium-D3 tablets is not considered to have any potential for single dose toxicity when used according to the restrictions specified in the SmPC.

The results of a study provide evidence to support the hypothesis that altered calcium homeostasis is indirectly involved in the pathogenesis of pheochromocytomas, via effects on chromaffin cell proliferation. It is however agreed with the applicant that since these observations were noted in rats at doses approx. 250-fold higher than those used in humans, the risk of having an impact clinically is low. In growing dogs, a dose 135-times higher than recommended decreased plasma PTH levels and increased plasma calcitonin levels. In animals as well as in humans, the toxic symptoms of chronic administration of high doses of vitamin D are like those reported to be associated with hypercalcaemia.

Medicinal products containing calcium and vitamin D have been available in Europe for decades and their use is well-established with recognised efficacy and acceptable safety.

Genotoxicity

-*Calcium*

No studies on genotoxicity and calcium have been identified by the Applicant.

-*Vitamin D*

Genotoxicity data from the literature indicate that cholecalciferol is not genotoxic.

Carcinogenicity

-*Calcium*

No preclinical data concerning the carcinogenic potential of Ca2+ were identified by the Applicant. Three human studies on the subject were however reported.

-*Vitamin D*

The carcinogenicity potential of cholecalciferol has been reviewed by the applicant. In short summary, the studies do not point to carcinogenic potential. It is agreed the data do not point to a carcinogenic potential.

Reproduction

-*Calcium*

High doses of Ca2 + were associated with reproductive toxicity in some species.

The observation from a study in male albino rats suggest that excessive dietary calcium enhances the generation of free- radicals resulting in structural and functional disruption of male reproduction. However, the doses used in this study far exceeds those used with Calcium-D3 tablets; it is thus agreed that no reproductive toxicity has to be expected based on the results of this study.

In another study in rats, calcium carbonate doses at about 400 - 1,200 mg/kg b.w./d, during 6 weeks before mating and for 20 days of gestation, did not reveal any toxic manifestations/signs to the foetuses.

In mice, high levels of maternal dietary calcium (ie 1.2% in the control diet with 3% calcium carbonate in the food and 4% calcium lactate in drinking water obtained at least 10 days before mating and during pregnancy) were associated with fetal toxicity. No difference in mortality per litter was noted, however, fetuses showed lower birth weights and retarded skeletal and dental calcification, which is evident from a significantly lower total calcification index.

Doses above 1,200 mg / kg b.w. were associated with signs of maternal and fetal toxicity. However, this dose is 120 times higher than the daily dose of Ca2 + given by calcium D3 tablets administered according to the SmPC. High doses of calcium in the diet are associated with reproductive toxicity, as evidenced by a variety of animal species. However, the relevant information is sufficiently represented in the SmPC.

-*Vitamin D*

Functional animal model studies have shown that vitamin D is important for sex steroid production, oestrogen signalling, and semen quality.

Male and female rats pre-exposed to 1,25- (OH) 2D3 (0.02, 0.08 or 0.3 µg / kg b.w./d) showed no evidence of impaired fertility or that this exposure would be teratogenic. In rabbits, dosages of 0.3 µg/kg/day produce maternal and foetal toxicity, doses approximately 8x the human exposure.

In another study, pregnant albino rats were given 20,000 or 40,000 IU of vitamin D2 per day by intragastric intubation from the 10th to the 21st day of gestation. There was a marked reduction in the weight of the new-born of the experimental rats as compared to the offspring of control rats which did not receive vitamin D2 - this weight difference between the offspring of the two groups became greater over the subsequent weeks. Furthermore, osteogenesis of the long bones was impaired in the offspring of the experimental rats, as evidenced by retarded epiphyseal ossification and persistence of enchondral bone trabeculae within the diaphysis. There was another study indicates a similar result that high doses of vitamin D during pregnancy was associated with growth retardation of the rat pups**.** Increased foetal mortality was noted in offspring to rabbits that were given 14,000 - 1,400,000 IU vitamin D2 or placebo i.m. during the pregnancy. In yet another study on rabbits, where vitamin D2 (750,000 IU) was administered by i.m. injection to the mother during pregnancy, cranial, facial and dental peculiarities, notably severe malocclusion of the teeth was noted in the offspring.

The preclinical data suggests that overdoses of vitamin D should be avoided in pregnancy. Available clinical experience supporting the safe use of relatively high doses of vitamin D (in combination with calcium) supplementation in pregnancy and lactation is insufficient to assess the potential risk, particularly regarding long term use.

The Non-clinical Overview on the pre-clinical toxicology is considered sufficient.

Environmental Risk Assessment (ERA)
It is agreed that since Calcium Vitamin D3 contains vitamins and electrolytes, there is a low risk of environmental impact. The current ERA is thus accepted.

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 Applicant has provided a relevant discussion of the issue, comparing their formulation to other approved formulations, and discussed relevant clinical aspects. In addition, in vitro dissolution data has been provided which is assessed in the quality section. The product will be taken as a complement to dietary calcium and vitamin D3, which might be highly variable, and the patient response to treatment should be monitored. 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 plasma levels of calcium and vitamin D3 are 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. From a pharmacokinetic point of view, it is acceptable to use quality data to establish a bridge to the literature.

The pharmacokinetics of calcium and cholecalciferol has generally been sufficiently described and claims in the SmPC supported by adequate references.

Pharmacodynamics
Cholecalciferol (vitamin D3) is a liposoluble pro-hormone formed in the skin on exposure to UV light and converted into its biologically active form, 1,25-dihydroxycolecalciferol, in two hydroxylation steps, first in the liver (position 25) and then in the renal tissue. Vitamin D is required to maintain normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralization of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D achieves this after its conversion to the active form1,25-dihydroxyvitaminD [1,25-(OH)2D],or calcitriol. This active form regulates the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins. Ionized calcium is the necessary plasma fraction for normal physiologic processes. In the neuromuscular system, ionized calcium facilitates nerve conduction, muscle contraction, and muscle relaxation. Calcium is necessary for bone mineralization and is an important cofactor for hormonal secretion in endocrine organs. At the cellular level, calcium is an important regulator of ion transport and membrane integrity.

Calcium is required for normal growth and development of the skeleton. During skeletal growth and maturation, calcium accumulates in the skeleton at an average rate of 150 mg/d. During maturity, the body – and therefore the skeleton – is more or less in calcium equilibrium. From the age of about 50 in men and from the menopause in women, bone balance becomes negative and bone is lost from all skeletal sites. This bone loss is associated with a marked rise in fracture rates in both sexes, but particularly in women. Adequate calcium intake modifies the rate of bone loss associated with ageing.

A drastic change in the plasma calcium concentration, either a decrease (hypocalcemia) or increase (hypercalcemia), is lethal; therefore, calcium level is tightly regulated by several hormones, which are three classical calcium-regulating hormones, namely parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], and calcitonin, as well as some other endocrine or paracrine factors [e.g., estrogen, prolactin, insulin-like growth factor-1, and fibroblast growth factor-23].

Vitamin D (Cholecalciferol) is an important factor in maintaining intracellular and extracellular calcium concentrations within a physiological range. Cholecalciferol thus significantly contributes to

maintain bone structure and function. erum 1,25-vitamin D levels are significantly lower in obese than non- obese subjects. Reduced cholecalciferol formation in the skin is common, especially in elderly people and during the winter.

Pharmacodynamic Interactions
Calcium complexes tetracycline antibiotics rendering them inactive; the two drugs should not be given at the same time orally nor should they be mixed for parenteral administration.
The inotropic and toxic effects of cardiac glycosides and calcium are synergistic and arrhythmia may occur if these drugs are given together (particularly when calcium is given i.v.)
Corticosteroids counteract the effects of cholecalciferol. Concurrent use of cholecalciferol and cardiac glycosides may result in cardiac arrhythmia. The possible interactions of calcium and cholecalciferol with other substances are all reflected in the SmPC for Calcium-D3. Some interactions of cholecalciferol, e.g. with heart glycosides, might be attributed to calcium rather than to cholecalciferol. As the present formulation is intended for oral administration and is aimed to replete deficient stores, e.g. due to insufficient sun exposure in combination with other risk factors, it can be assumed that the risk of severe systemic interactions is low if the product is taken as indicated.

Clinical efficacy
The medical use of vitamin D/calcium supplementation is reflected by several published clinical studies. Particularly, the combination of 2,000 IU of vitamin D3 and 500 mg of calcium has been already investigated in a clinical study in Denmark published in 1984.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 of vitamin D and calcium deficiency in the elderly. 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).

Clinical safety
Vitamin D and calcium are natural food components and have been administered as supplementation to natural intake for several decades. These medicinal substances are well known. Risk of intoxication is not foreseen for recommended daily doses of 500 mg calcium and 2000 IU vitamin D in the proposed indications. Once daily dosing is accepted. The chewable tablet 500mg / 2000 IU has a higher vitamin D content than most of the previously approved combination products with these substances. However, a product with the same composition and strength is already approved (SE/H/1777/01-02/D). Furthermore. as a monoproduct, the strength 2000 IU/day of vitamin D is approved for treatment of vitamin D deficiency. 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 Vitamin D3.

Safety specification

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 01-Mar-2022 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to CACIT® VITAMINE D3 500 mg/440 UI, DE/H/5016/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Calcium and cholecalciferol (vitamin D3) are both physiological agents which are essential for bone mineralisation. A sufficient dietary intake of calcium and adequate concentrations of vitamin D are needed to prevent bone mineral release. If calcium and vitamin D levels fall below the physiological requirements and international recommendations, a supplementation of calcium and vitamin D to

vitamin D deficient subjects, is recommended by expert consensus. Risk of intoxication is considered low for recommended dose in the proposed indication.

There are no objections to approval of Calcium/Cholecalciferol Theramex, from a quality, non-clinical and clinical point of view. There are some remaining uncertainties with regard to bridging to literature data as there are apparently no chewable tablets with this exact formulation and strength referred to. This is nevertheless not deemed crucial as the literature covers a broad range of products without any evidence for difference in performance following differences in formulation. The data provided by the applicant in the last round of assessment gives further support to the application as it can be confirmed that there is at least one similar product approved on the EU market. However, the applicant has accepted to conduct further dissolution profile comparisons and provide data prior to the product being placed on the market.

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

Description	Due date
Conduct a dissolution profile comparison with a product tested in the efficacy studies alternatively an adequate market leader. Data will be provided prior product being placed on the market.	3 months after D210

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/2000 IE, chewable tablet was positively finalised on 2023-07-19.

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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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