CBG MEB

Public Assessment Report

Scientific discussion

Calcium/Vitamine D3 Sandoz 500 mg/440 IU, chewing tablets

(calcium carbonate/ cholecalciferol concentrate)

NL/H/4093/001/DC

Date: 14 August 2017

This module reflects the scientific discussion for the approval of Calcium/Vitamine D3 Sandoz 500 mg/440 IU, chewing tablets. The procedure was finalised on 17 June 2014 with Germany as RMS (DE/H/3742/001/DC). The current RMS is the Netherlands (NL/H/4093/001/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Calcium/Vitamine D3 Sandoz 500 mg/440 IU, chewing tablets, from Sandoz B.V.

The product is indicated:

- for the prevention and treatment of vitamin D and calcium deficiency in older people,
- as vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

A comprehensive description of the indications and posology is given in the SmPC.

This decentral procedure concerns a bibliographical application based on well-established medicinal use of chewing tablets containing the active substances calcium and vitamin D3. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

Administration of calcium and vitamin D3 simultaneously as single agents or as fixed combination has been in clinical use for decades. It has proven to be both sufficiently safe and effective in the prophylaxis and clinical treatment of the respective mineral and hormone deficiency potentially leading to or worsening osteoporosis. A number of studies and reviews clearly indicated that calcium and cholecalciferol have positive effects on calcium homeostasis and bone mineralisation, and can be used in states of deficiency and for supportive treatment of osteoporosis. Supplementation of patients with diagnosed deficiency of calcium and vitamin D with Calcium-Vitamin D3 chewable tablets helps preventing detrimental bone resorption and is therefore justified as a supportive treatment for osteoporosis.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The RMS of the initial procedure was Germany, and the concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Ireland, the Netherlands, Poland and the Slovak Republic.

II. QUALITY ASPECTS

II.1 Introduction

Calcium/Vitamine D3 Sandoz is a round, white, chewable tablet with a faultless surface. Each chewable tablet contains 1250 mg of calcium carbonate (equivalent to 500 mg of calcium) and (4.4 mg of cholecalciferol concentrate (equivalent to 11 micrograms of cholecalciferol or 440 IU of vitamin D3).

The chewable tablets are packed in strips of laminated aluminium paper foil

The excipients are: isomalt (E953), xylitol, sorbitol (E420), anhydrous citric acid, sodium dihydrogen citrate, magnesium stearate, carmellose sodium, flavour Orange “CPB” (containing natural orange oil concentrate, natural/nature identical mandarine oil, natural/nature identical liquid flavour tropical fruit,

natural/nature identical orange oil, natural/nature identical solid flavour multifruit, mannitol (E421), maltodextrin, gluconolactone, sorbitol (E420)), Flavour Orange “CVT” (containing natural orange oil, natural mandarine oil, nature identical powder flavour orange, mannitol (E421), gluconolactone, sorbitol (E420), medium-chained triglyceride), aspartame (E952), acesulfam potassium, sodium ascorbate, all-rac-alpha-tocopherol, modified (maize) starch, sucrose, medium chain triglycerides and colloidal anhydrous silica.

II.2 Drug Substances

Calcium carbonate
One of the two active substances is calcium carbonate, an established active substance, described in the European Pharmacopoeia (Ph. Eur.). It is a white powder and practically insoluble in water.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with an additional testing for nitrates. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Cholecalciferol concentrate
The second active substance is cholecalciferol concentrate (powder form), an established active substance, described in the European Pharmacopoeia (Ph. Eur.). It is a white or yellowish-white powder with small particles which, depending on their formulation, may be practically insoluble in water or may swell or form a dispersion.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Cholecalciferol concentrate (powder form) is manufactured by standard procedures using standard production equipment. The ASMF of Cholecalciferol concentrate (powder form) has been accepted.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The control tests and specifications for drug substances product are adequately drawn up. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
Stability studies have been performed. The proposed retest period is 24 months from the date of manufacture in the unopened original container and at a temperature below 15 °C. Keep container tightly closed. Once opened, use contents quickly.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained

Manufacturing process
The manufacturing process has been validated according to relevant guidelines. Process validation data on the product have been presented in accordance with the relevant European guidelines.

Control of excipients
The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches in accordance with the ICH stability guideline. The batches were stored in the proposed packaging. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC or on the label. Photostability studies are in accordance with “Note for Guidance on the Photostability testing of New Active Substances and Medical products” (CPMP/ICH/279/95) have been provided.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Calcium/Vitamine D3 Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The approval of this product will not result in an increase in the total quantity of the active substances released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of vitamin D and calcium as well as the combination of both, are well known are well known. As the combination of these active substances acid are widely used and well-known, no further studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcium carbonate and cholecalciferol concentrate (vitamin D3) are well-known active substances with established efficacy and tolerability. The dossier is based on well-established use of these active substances. The MAH summited a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

IV.2 Pharmacokinetics

Calcium

Absorption

30-40% of the ingested dose of calcium is absorbed, predominantly in the proximal part of the small intestine.

Distribution and biotransformation

99% of the calcium in the body is concentrated in the mineral component of bones and teeth. The remaining 1% is present in the intra- and extracellular fluids. About 50% of the total blood-calcium content is in the physiologically active ionised form with approximately 5% being complexed to citrate, phosphate or other anions. The remaining 45% are being bound to proteins, principally albumin.

Elimination

Calcium is excreted in the urine, faeces and in sweat. Urinary excretion depends on glomerular filtration and tubular resorption.

Vitamin D3

Absorption

Vitamin D3 is absorbed in the intestine.

Distribution and biotransformation

Vitamin D3 is transported by protein binding in the blood to the liver (where it undergoes the first hydroxylation to 25-hydroxycholecalciferol) and to the kidneys (second hydroxylation to 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D3). Non-hydroxylated vitamin D3 is stored in muscle and adipose tissues.

Elimination

The plasma half-life is in the order of several days; vitamin D3 is eliminated in the faeces and urine.

IV.3 Pharmacodynamics

Mechanism of action

Calcium/Vitamine D3 Sandoz is a fixed combination of calcium and vitamin D3. The high calcium and vitamin D3 concentration in each dose unit enables sufficient absorption of calcium with a limited number of doses. Vitamin D3 is involved in calcium-phosphorus metabolism. It allows the active absorption of calcium and phosphorus from the intestine and their uptake by bone. Supplementation with calcium and vitamin D3 corrects latent vitamin D deficiency and secondary hyperparathyroidism.

Pharmacodynamic effects

In a double-blind placebo controlled study of 18 months, including 3,270 women aged 84±6 and living in nursing homes, supplemented with cholecalciferol (800 IU/day) + calcium (1.2 g/day), a significant decrease in PTH secretion has been observed. After 18 months, the results of the intent to treat analysis showed 80 hip fractures in the calcium vitamin D group and 110 hip fractures in the placebo-group (p=0.004). So in the conditions of this study, the treatment of 1,387 women prevented 30 hip fractures. After 36 months of follow-up, 137 women presented at least one hip fracture in the calcium-vitamin D group (n=1,176) and 178 in the placebo group (n=1,127) (p≤0.02).

IV.4 Clinical efficacy

The indications for calcium–D3 are widely established for products containing combinations of calcium and vitamin D, and such products are recognised as being of therapeutic value. Thus, it is unlikely that additional clinical trials with calcium- D3 will result in a reassessment of the efficacy of this product for these indications. A summary of the currently available bibliographic data on the use of calcium and vitamin D justifies the use in these indications and for the authorised posology.

IV.5 Clinical safety

Calcium and vitamin D are substances that are necessary for normal body function and are carefully regulated to remain within the physiological concentration range. Supplementation of calcium and vitamin D to patients who are deficient in these substances and who are at risk of bone loss or fracture is therefore generally well tolerated and is of great potential benefit in this population. Calcium-D3 tablets already being on the EU market are well tolerated in the vast majority of patients.
Overdose can lead to hypervitaminosis, hypercalciuria and hypercalcaemia. Therefore, the administration of Calcium-Sandoz D Osteo 500 mg / 440 I.E. is contraindicated in patients with conditions with an increased risk for these complications such as patients with nephrolithiasis, nephrocalcinosis, severe renal impairment or primary hyperparathyreoidism. Interactions with other medicinal products are known (e.g. thiazide diuretics, corticosteroids, phenytoin, cardiac glycosides) and in case of increased risk of hypercalcaemia regular monitoring of serum calcium is needed.

IV.6 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/Vitamine D3 Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypercalcaemia • Hypervitaminosis D (particularly in patients with sarcoidosis, pregnant women, renal impaired patients) • Hypersensitivity reactions (including laryngeal oedema and angioedema) • Nephrolithiasis/Nephrocalcinosis • Burnett syndrome • Interaction with bisphosphonates, sodium fluoride, levothyroxine, oxalic acid • Increased risk of hypercalcaemia due to interaction with thiazide diuretics • Increased toxicity of cardiac glycosides due to hypercalcaemia
Important potential risks	• Cardiovascular events • Overdose due to calcium and vitamin D intake from other sources like food or food supplements • Potential of paediatric off-label use
Missing information	

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on clinical aspects

Reference is made to relevant published clinical data in order to assess the clinical efficacy and safety of the combination calcium carbonate and cholecalciferol.
Clinical studies have shown that the combination of both substances is sufficiently effective and safe for the prevention and treatment of vitamin D and calcium deficiency in elderly patients and as vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk

of vitamin D and calcium deficiency. Extensive and long-term experience in clinical practice confirms acceptable safe and effective use of preparations containing combinations of calcium and vitamin D3.

V. USER CONSULTATION

A user consultation with target patient groups on the package (PL) has been performed on the basis of a bridging report making reference to Calcium 600 Vitamin D 400 Hermes, chewable tablets and Calcium 1000 mg / Vitamin D3 880 IU, chewable tablets (DCP:DE/H/2858/01). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Calcium/Vitamine D3 Sandoz 500 mg/440 IU, chewing tablets has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The quality of starting material, active substance and finished product as well as the manufacturing, quality control and stability can be considered as sufficient.

From a clinical point of view, the proposed indications, as well as the proposed posology, are in line with current calcium and vitamin D3 use and recommendations in the RMS and CMS countries, in which this type of product has been registered for many years. Based upon clinical data and longstanding clinical experience, the use of this product in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Calcium/Vitamine D3 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
DE/H/3742/1/IA/001	Addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing	-	22-12-2014	Approval	-
DE/H/3742/IB/002/G	- Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier; extension or introduction of a re-test period/storage period supported by real time data - Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient; New certificate from a new manufacturer (replacement or addition)	SmPC	03-03-2015	Approval	-
DE/H/3742/1/IB/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	SmPC PL	04-03-2015	Approval	Adjustment according to CSP of AT/H/PSUR/0040/001