COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Calcin D3 500 mg/400 IU and Calcin D3 Forte 500 mg/800 IU chewable tablets

(calcium carbonate/cholecalciferol)

NL/H/4463/001-002/DC

Date: 27 May 2020

This module reflects the scientific discussion for the approval of Calcin D3 500 mg/400 IE and Calcin D3 Forte 500 mg/800 IE chewable tablets. The procedure was finalised at 29 July 2019. 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 Calcin D3 500 mg/400 IE and Calcin D3 Forte 500 mg/800 IE chewable tablets, from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

The product is indicated for:

- Prevention and treatment of calcium and vitamin D deficiency in adults and elderly.
- Vitamin D and calcium supplement in addition to specific osteoporosis treatment of adults who are at risk of vitamin D and calcium deficiency.

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

This decentralised 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 concerned member states (CMS) involved in this procedure were Cyprus and Greece.

II. QUALITY ASPECTS

II.1 Introduction

- Calcin D3 is a white round chewable tablet and contains calcium carbonate equivalent to 500 mg calcium and cholecalciferol concentrate (powder form) equivalent to 400 IU (10 microgram) cholecalciferol (vitamin D_3).
- Calcin D3 Forte is a white, round, chewable tablet, engraved with the word "Forte" in one side. Each tablet contains calcium carbonate equivalent to 500 mg calcium and cholecalciferol concentrate (powder form) equivalent to 800 IU (20 microgram) cholecalciferol (vitamin D_3).

The chewable tablets are packed in white, opaque Al/PE blister (Al, LDPE).

The excipients are: Povidone (E1201), sodium ascorbate, all rac-a-tocopherol (E 307), modified starch, sucrose, medium chain triglycerides, silicon dioxide colloidal, sorbitol (E 420), mannitol (E 421), talc, citric acid (E 330), sodium cyclamate (E952), magnesium stearate, orange flavour, tangerine flavour, maltodextrin (maize) and modified starch E1450 (waxy maize).

II.2 Drug Substances

The active substances are calcium carbonate and cholecalciferol concentrate (powder form); both established active substances described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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 Ph.Eur.

Calcium carbonate
Calcium carbonate is white or almost white powder and practically insoluble in water.

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 CEP. According to the CEP no tests are deemed necessary in addition to those of the Ph. Eur. monograph. Batch analytical data demonstrating compliance with this specification have been provided for one production scaled batch and the results of two other batches are considered covered by the CEP.

Stability of drug substance
The active substance is stable for 1 year when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Cholecalciferol concentrate (powder form)
Cholecalciferol concentrate (powder form) are white or yellowish-white small particles. The active substance is practically insoluble and swells or forms a dispersion in water, depending on the formulation.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included. However, as the CEP related to an active substance mix, the MAH has provided information concerning the description of the manufacturing process for preparation of the mixture and stability data of the mixture.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEP, with additional requirements to those of the Ph.Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for appropriate number of batches.

Stability of drug substance
The active substance is stable for 1 year when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The dose levels are within the dosage range commonly used in clinical practice. The fixed dose combination may increase the adherence and compliance to the treatment. The chewable tablets are considered a suitable dosage form. A justification has been provided on how the characteristics of the formulation were adapted to be suitable as a chewable tablet.

Manufacturing process

The manufacturing process consists of granulation, blending and tabletting and has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for five full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The proposed specifications for the excipients are acceptable. Acceptable information on the composition and identity testing of the flavours was provided by the supplier.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of both active substances, assay of both active substances, average weight, resistance to crushing, friability, uniformity of dosage units for both active substances, water content, disintegration and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release limits are generally identical to those proposed for shelf-life. Moisture content is tested at release only; this is acceptable considering the stability data. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from five 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 five full-scale batches stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies in accordance with ICH recommendations are not available. Considering the sensitivity for light of cholecalciferol, the product should be stored in the original packaging for protection from light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: 'This medicinal product does not require any special temperature storage conditions. Store in the original package, in order to protect from moisture and light.'

Specific measures concerning 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 Calcin D3 and Calcin D3 Forte have 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. The product 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. As the combination of these active substances is 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

An overview of formulations used in the literature was submitted. Although the proposed formulations contain excipients that may affect absorption (i.e. sorbitol and mannitol), a discussion has been provided that the amounts are considered not to affect pharmacokinetics. The amounts mentioned however are at the high end, and it is known that even at low amounts of sorbitol/mannitol, an effect can occur and this may be drug specific. However, the MAH refers to formulations used in literature also containing sorbitol/mannitol. Moreover, disintegration time data showed that release of the actives is within that of the formulations in literature. Taking into account the provided literature data, a clinically relevant difference in bioavailability is not expected.

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been conducted and none are needed for this well-established use application. The MAH has submitted bibliographic data up to 2016. None of the studies reported safety problems, e.g. hypercalcaemia.

IV.4 Clinical efficacy

In order to demonstrate the efficacy of calcium and cholecalciferol in patients with vitamin D deficiency or subjects who are at high risk for vitamin D deficiency, the MAH provided several publications, including meta-analyses.

It is accepted that the use of cholecalciferol and calcium for the prevention and treatment of vitamin D and/or calcium deficiency and as supportive treatment for osteoporosis is well established.
Large scale population studies show that low serum 25OHD is associated with a number of adverse outcomes in the human musculoskeletal, innate immune and cardiovascular systems. An adequate calcium intake, mostly in the form of calcium supplements, is recognized as essential co-therapy in the treatment of osteoporosis.
A causal relationship between vitamin D and musculoskeletal health has been well-established. Vitamin D and calcium deficiency can cause rickets in children and osteomalacia in adults and may contribute, with other factors, to osteoporosis, falls and frailty in the elderly.

IV.5 Clinical safety

The safety profile of calcium and cholecalciferol is well-known. In general, calcium and vitamin D are well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia and hypercalciuria are the main adverse events.

In general, the description of safety in the clinical overview is considered sufficient. The following adverse events are mentioned in the SmPC for approved calcium/vitamin D products: hypercalcaemia, hypercalciuria, constipation, flatulence, nausea, abdominal pain, diarrhoea, milk-alkali syndrome, hyperphosphatemia, nephrolithiasis, nephrocalcinosis and hypersensitivity reactions such as pruritus, rash, urticaria.

The SmPC as proposed is considered acceptable

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 Calcin D3 and Calcin D3 Forte.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient.

IV.7 Discussion on the 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.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Calcin D3 500 mg/400 IE and Calcin D3 Forte 500 mg/800 IE chewable tablets have 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 efficacy and safety was shown, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 July 2019.

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