CBG MEB

Public Assessment Report

Scientific discussion

Calcium and Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules

(calcium carbonate and cholecalciferol)

NL License RVG: 111783

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This module reflects the scientific discussion for the approval of Calcium en Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules. The marketing authorisation was granted on 3 October 2015. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Calcium and Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules from Alpex Pharma (UK) Limited.

The product is indicated for:

- Correction of combined calcium and vitamin D deficiency in elderly patients.
- Calcium and vitamin D supplementation as an adjunct to specific therapy for osteoporosis, in patients with an established increased risk of combined calcium and vitamin D deficiency.

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

Vitamin D increases the intestinal absorption of calcium. Vitamin D supplementation corrects an insufficient vitamin D intake.
Oral intake of calcium supplementation corrects a deficiency of calcium in the diet and supports the remineralisation of the skeleton if there is a lack of calcium in the diet.
Oral intake of vitamin D_3 corrects a vitamin D deficiency when both intake of vitamin D and sunlight exposure are inadequate. Vitamin D increases the intestinal absorption of calcium.
Combined calcium and vitamin D_3 administration corrects secondary senile hyperparathyroidism by counteracting the increase in parathyroid hormone (PTH) which is caused by calcium and vitamin D_3 deficiency and which causes increased bone resorption.

Products containing fixed combinations of calcium and vitamin D have been in use for several decades and there are currently a number of products on the market that contain the same amounts or similar proportions of calcium and vitamin D as in the proposed product. These products have the same indications.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of calcium carbonate and vitamin D_3.

II. QUALITY ASPECTS

II.1 Introduction

Calcium and Vitamine D3 Alpex 1000 mg/880 IE contains per sachet 2500 mg calcium carbonate, corresponding to 1000 mg calcium, and cholecalciferol concentrate powder corresponding to 880 IE (equivalent to 22 µg of vitamin D_3).
The product is an effervescent granulate with white to off-white effervescent granules, divided in sachets.

Excipients are citric acid, maltodextrin, lemon-lime flavour, sucralose, modified starch, silica colloidal anhydrous (Aerosil 200), sucrose, sodium ascorbate, medium chain triglycerides, silicon dioxide and alpha-tocopherol.

The effervescent granulate is packed in in paper/PE/Al/PE sachets.

II.2 Drug Substances

The active substances are calcium carbonate and cholecalciferol (vitamin D_3), established active substances, described in the European Pharmacopoeia (Ph.Eur.). Calcium carbonate is a well known established inorganic salt in the form of a white or almost white powder, which is practically insoluble in water. Cholecalciferol is a well known established vitamin (D_3) in the form of white or almost white crystals that are practically insoluble in water, but freely soluble in ethanol 96%. A powder concentrate is manufactured.

The CEP procedure is used for the 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.

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

Quality control of drug substance
The drug substance specifications for calcium carbonate and cholecalciferol have been provided and are in compliance with the Ph.Eur.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches of calcium carbonate, and three full-scale batches of cholecalciferol concentrate.

Stability of drug substance
For calcium carbonate a retest period of 1 year is claimed and supporting stability data have been provided.
Stability data on the active substance cholecalciferol concentrate have been provided for three full-scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). No trends or out of specification results were observed during the stability studies.
The retest period of 60 months with the storage condition “Store in the unopened original container and at a temperature of 5°C ± 3°C” is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Since the test product is an aqueous oral solution at the time of administration and it contains active substances in the same concentrations as approved oral solutions, the bioequivalence study may waived according to the Guideline on the investigation of bioequivalence. Thus, from a chemical pharmaceutical point of view the test and reference products, described in literature, are bio-equivalent and no further bioequivalence studies are required.
A formulation study has been performed in order to formulate an effervescent product with the following general characteristics:

- aspect of the granular: white without foreign bodies
- weight of the sachets
- effervescent granular which completely dissolves in about 200 ml tap water
- pH of the drinking solution between 4 and 5.

The MAH adequately demonstrated that the test and reference product both dissolved within 5 minutes. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
A non standard manufacturing process has been employed based on the amount of cholecalciferol in the final drug product.
The whole process may be subdivided in three main steps: granulation, blending and packaging.
The manufacturing process has been validated on three full-scale batches demonstrating that the process is adequate to manufacture the product consistently.

Control of excipients
Almost all of the excipients comply with the Ph.Eur. These specifications are acceptable. The lemon-lime flavour has in house specifications. The specification is acceptable.
A specification for the cholecalciferol concentrate has been provided and is in line with the Ph.Eur. monograph.

Quality control of drug product
The product specification includes tests for appearance of granules, solution and sachets, pH of the solution, average weight, loss on drying, identification of calcium and cholecalciferol, assay of calcium and cholecalciferol, seal test, uniformity of dosage units and microbiological characteristics.
Furthermore a forced degradation study demonstrated the stability indicating capabilities of the assay methods.
There is no difference between the release and shelf-life specification. The analytical methods included in the specification have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in paper/PE/Al/PE sachets. Exposure to UV light did not show degradation.
Based on the submitted data the proposed shelf life of 24 months stored in a paper/PE/Al/PE sachet with the storage condition 'store below 25°C' is acceptable. Post approval the shelf life was extended to 36 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
On the CEP of cholecalciferol it is mentioned that sheep wool is used in the manufacturing of the drug substance. However, it meets the criteria described in Ph.Eur. monograph *Products with risk of transmitting agents of animal spongiform encephalopathies* as mentioned on the CEP.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Calcium and Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Calcium and Vitamine D3 Alpex 1000 mg/880 IE is intended as a substitute for other identical products on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The application for Calcium and Vitamine D3 Alpex is based on well-established use. This is endorsed, since calcium carbonate and cholecalciferol have been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcium carbonate and cholecalciferol are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview

justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

The pharmacokinetics of calcium carbonate and cholecalciferol (vitamin D) are well known. The overview of pharmacokinetics is based on published studies addressing in general the pharmacokinetics of formulations containing either calcium or vitamin D alone.

In the stomach, calcium carbonate releases calcium ions depending upon pH. Calcium administered as calcium carbonate is absorbed to the extent of 20-30% and the absorption takes place mainly in the duodenum through vitamin D-dependent, saturable, active transport. Almost all calcium in the body is concentrated in the hard structure of bones and teeth. The remaining part (about 1%) is distributed over the intra- and extracellular fluids. About 50% of the total blood-calcium content is in the physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.
Calcium is eliminated via faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin D is absorbed in the small intestine. Cholecalciferol is converted in the liver by hydroxylation to 25-hydroxycholecalciferol. It is then further converted in the kidneys to the active form 1,25 dihydroxy cholecalciferol. 1,25 dihydroxy cholecalciferol is the metabolite responsible for increasing calcium absorption. Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is distributed to adipose and muscle tissues and is excreted in faeces and urine.

The Calcium and Vitamin D3 Alpex 1000 mg/880 IE effervescent granules should be dissolved in a glass of water to obtain a solution before intake. Dissolution data at pH 1.2, 4.5 and 6.8 (500 ml) showed very rapid dissolution, i.e. 100% within 5 min, of calcium and vitamin D_3.

The formulation does not contain excipients which are considered to affect absorption in a clinical relevant way. Sucralose may have some iso-osmotic properties, however the content is low. In addition, considering other calcium/vitamin D registered formulations, a wide range of excipients are used, of which sorbitol and mannitol.

Considering that this is a bibliographic application, the granules should be dissolved before intake as a solution and the excipients are considered not to affect absorption clinically relevant, literature data can be bridged to this formulation.

IV.3 Pharmacodynamics

Calcium and vitamin D have been available on the European market for over many years. No new data were submitted nor a detailed overview on primary and secondary pharmacology based on literature references. This sufficiently substantiates the well-established use of both active substances regarding pharmacology.
Both calcium and vitamin D are essential nutrients for bone health. Vitamin D plays an important role in the maintenance of calcium blood levels and bone mineralisation by promotion of the intestinal absorption and renal reabsorption of calcium. Passive functions such as activation of enzymes that play a role in digestion, in the blood coagulation cascade, or in immune defense are little affected by changes in plasma calcium concentrations. Active functions are sensitive to changes in extracellular calcium levels.

IV.4 Clinical efficacy

Calcium and vitamin D are well-known active substances and considered well-established use in the prevention and treatment of calcium and vitamin D deficiency in elderly patients and as an adjunct to specific therapy in the prevention and treatment of osteoporosis for patients who are at risk of calcium and vitamin D deficiency. Various products containing calcium and vitamin D at the same strengths are licensed for over 10 years. Clinical efficacy is supported by the literature references submitted by the MAH, although studies of vitamin D and calcium for fracture prevention have produced inconsistent results. This most likely results from different vitamin D status and calcium intake at

baseline, different doses and poor to adequate compliance[1]. Literature data support the proposed daily dose of calcium and vitamin D.

IV.5 Clinical safety

Supplementation with a combination of calcium and vitamin D is a well established therapy in elderly patients and has been practised for many years. Adverse events are well characterised. The daily dose with this regimen corresponds to current recommendations.

IV.6 Risk Management Plan

The MAH did not submit a risk management plan, as it was not required at the time the application was made. This is acceptable. Both active substances are well known.
The MAH has a pharmacovigilance system in place, in compliance with the applicable guidelines.

IV.7 Discussion on the clinical aspects

Calcium and Vitamine D3 Alpex is considered widely established. For this authorisation, reference is made to clinical studies and experience with calcium carbonate and cholecalciferol. The product has been shown to be effective in the treatment of the stated indications. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The text of the PL is the same as already approved and in force for the reference medicinal product CaD 1000/880 citroen, effervescent granules. The lay-out and style of the proposed PL is also very similar to the PL of the reference product. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Calcium and Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules has a proven chemical-pharmaceutical quality. Calcium and Vitamine D3 Alpex is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Calcium and Vitamine D3 Alpex 1000 mg/880 IE, effervescent granules was authorised in the Netherlands on 3 October 2013.

[1] Lips P., et al. Reducing fracture risk with calcium and vitamin D. Clin. Endocrinol 2010; 73: 277-85.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Extension of the shelf-life of finished product from 24 to 36 months.	IB	24-10-2014	10-12-2014	Approval	No
Change in the batch size of the finished product up to 10-fold compared to the originally approved batch size.	IA	11-11-2014	11-12-2014	Approval	No
Change in address MAH and SmPC update	IA	29-09-2015	26-10-2015	Approval	No
PL update	IA	22-12-2015	04-01-2016	Approval	No
SmPC update	IA	17-03-2016	04-04-2016	Approval	No
Databank update	IA	12-06-2017	22-06-2017	Approval	No