

Public Assessment Report Scientific discussion

**Calcichew-D3, chewable tablet 1000 mg/800 IU
and
Calci-D3, film-coated tablet 500 mg/400 IU**

SE/H/126/02-03/DC

This module reflects the scientific discussion for the approval of Calcichew-D3 1000 mg/800 IU/Calci-D3. The procedure was finalised on 4 June 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Nycomed Pharma AS has applied for marketing authorisations for Calcichew-D3 1000 mg/800 IU chewable tablet and Calci-D3 500 mg/400 IU film-coated tablet. The active substances calcium and vitamin D3 (cholecalciferol) are the same as previously approved Calcichew-D3 500 mg/400 IU chewable tablet marketed by Nycomed Pharma AS since 1996. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Calcichew-D3 1000 mg/800 IU is presented in the form of chewable tablets containing 1000 mg of calcium carbonate and 800 IU (20 mikrogram) of cholecalciferol. The excipients are sorbitol, lemon flavour granulate, povidone, magnesium stearate and aspartame. The tablets are packed in HDPE containers or PVC/PE/PVDC/Aluminium blisters.

Calci-D3 is presented in the form of film-coated tablets containing 500 mg of calcium carbonate and 400 IU (10 mikrogram) of cholecalciferol. The excipients are sorbitol, mannitol, acesulfame potassium, lemon flavour powder, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hypromellose, talc and propylene glycol. The tablets are packed in HDPE containers.

II.2 Drug Substance

Calcium carbonate:

Calcium carbonate has a monograph in the Ph Eur.

Calcium carbonate is a white powder.

The active substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

Cholecalciferol/Cholecalciferol concentrate (powder form):

Cholecalciferol concentrate (powder form) has a monograph in the Ph Eur.

Cholecalciferol concentrate (powder form) is a white or yellowish-white powder concentrate which is practically insoluble in water. The manufacturing process has been adequately described and satisfactory specifications have been provided for the powder ingredients.

The active substance specification includes relevant tests and the limits. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Calcichew-D3 1000 mg/800 IU:

Calcichew-D3 1000 mg/800 IU chewable tablet is formulated using excipients described in the current Ph Eur, except for lemon flavour granulate which is controlled according to acceptable in house specifications. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC when stored below 30°C and protected from light and moisture (in HDPE-containers) or when stored below 25°C and protected from light and moisture (in blisters).

Calci-D3:

Calci-D3 film-coated tablet is formulated using excipients described in the current Ph Eur, except for lemon flavour powder which is controlled according to acceptable in house specifications. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substances.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C and protected from moisture.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new data have been presented that alter the non-clinical assessment for these line extensions compared with the previously approved Calcichew-D3 500 mg/10 µg chewable tablet. Thus, a specific non-clinical assessment report has not been prepared. The Non-clinical Overviews and the literature data in module 4 for the previously approved tablet are considered to be valid also for Calcichew-D3 1000 mg/800 IU chewable tablet and Calci-D3 film-coated tablet. The active substances are the same and the recommended daily dose levels are similar. In Calcichew-D3 1000 mg/800 IU chewable tablet, the excipients are the same as in the previously approved chewable tablet. The excipients used in the Calci-D3 film-coated tablet are all established pharmaceutical excipients. The overview was prepared by Dr Paul Baldrick (Head Regulatory Affairs, Pharmaceuticals, Covance laboratories Limited) and signed 8 July, 2002. The Applicant performed a literature search to find if relevant non-clinical data have emerged since the issue of the previous non-clinical overview, but no new data were found that would give reason for a re-evaluation of the non-clinical profile. The report includes 120 literature references.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcichew-D3 1000 mg/800 IU chewable tablet and Calci-D3 film-coated tablet are intended for prevention and treatment of vitamin D and calcium deficiency in the elderly 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.

Calcichew-D3 1000 mg/800 IU is a new, higher strength of the chewable tablet, intended for once daily administration as an alternative to the previously approved Calcichew-D3 chewable tablet, which is intended for twice daily administration. Calci-D3 is a new form of the chewable tablet, and is intended for twice daily administration. The film-coated tablet has been developed for use in dose-dispensing machines. Calci-D3 may be swallowed or chewed, while the previously approved Calcichew-D3 chewable tablet should be chewed or sucked.

IV.2 Pharmacokinetics

No new pharmacokinetic data have been submitted. It was not necessary to perform bioequivalence studies to compare the new formulations with the previously approved Calcichew-D3 chewable tablet.

The Calcichew-D3 1000 mg/800 IU chewable tablet has the same qualitative composition and the same ratios between amounts of active substance and excipients as the Calcichew-D3 chewable tablet. Calcichew-D3 1000 mg/800 IU and Calcichew-D3 are manufactured by the same manufacturer and process and the dissolution profiles are similar under identical conditions. Their release properties would be expected to be similar and, thus, once daily administration with Calcichew-D3 1000 mg/800 IU will provide the same total daily dose of calcium and vitamin D3 as twice daily administration with Calcichew-D3 chewable tablet. The Calci-D3 tablet is a simple IR formulation with well-known excipients. The dissolution profiles for Calcichew-D3 chewable tablet and Calci-D3 film-coated tablet are similar under identical conditions. The products are intended as complements to dietary calcium and vitamin D3, with the aim to increase the body deposit of calcium and D3 on a long-term basis. A potential minor difference in *in vivo* release properties from two dosage forms would not be expected to lead to a different therapeutic profile.

IV.3 Pharmacodynamics

Once daily versus twice daily administration

Calcium

Michaletti and Zartarian (1996) studied the calcium retention after administration of 1000 mg calcium according to two different schedules, one 500 mg calcium tablet morning and night or two 500 mg calcium tablets in the morning. Calcium retention was not significantly different when calcium was taken twice daily compared with once daily: 26.7 % versus 21.3 % after 7 days of treatment and 20.2 % versus 17.3 % after 14 days of treatment. In a study by Ivanovich et al (1967), only very high doses of calcium carbonate were likely to cause hypercalcaemia (single doses of 8 g and 12 g).

Vitamin D

As this vitamin is fat-soluble, the absorption and metabolism of vitamin D resembles that of fats and fatty acids. Vitamin D is incorporated into mixed micelles and is then absorbed by a non-saturable passive diffusion. The absorption is depending on bile acids. About 80 % of orally ingested vitamin D is normally absorbed in the duodenum and jejunum. Absorption is lower in elderly than in younger subjects (Pattanaungkul et al 2000). Clinical experience is considered to be relevant, in the absence of bioavailability studies comparing different doses of vitamin D. The dose of 800 IU vitamin D/day has in clinical studies been achieved by once- or twice-daily dosing. Irrespective of which of these dosing schedules that was used, meta-analysis of the use of calcium and vitamin D supplementation in prevention of fractures has indicated that a dose of 800 IU/day is required and this dose has been superior to 400 IU/day (Bischoff-Ferrari et al 2005). A study of Dawson-Hughes et al (1997) used once-daily dosing of vitamin D and this study showed a significant effect of the supplementation in reducing non-vertebral fractures.

Calcium+ vitamin D

Boonen et al in 2007 published a meta-analysis of placebo-controlled randomised controlled trials to examine the effect of combined vitamin D and calcium supplementation. More than 45.000 patients from 6 randomised controlled trials of vitamin D plus calcium supplementation were analysed. The pooled relative risk for hip fracture was 0.82 % (95 % CI, 0.71, 0.94), showing a significant 18 % risk reduction in hip fracture with the combined use of calcium and vitamin D supplementation compared with no supplementation. The conclusion of this paper is that vitamin D supplementation, about 800 IU daily, should be used together with about 1000 mg calcium daily in targeted populations. An adjusted indirect comparison in the same paper showed a statistically significant 25 % reduction in hip-fracture risk with calcium and vitamin D regimen compared with vitamin D alone (95 % CI, 0.58, 0.06).

Osterberg and Blaschke (2005) found that as simple dosing schedule as possible improves adherence to therapy and Claxton et al (2001) found that adherence is inversely proportional to frequency of dosing.

IV.4 Clinical efficacy

Apart from the literature data supporting once-daily dosing, no new clinical data have been submitted. As this is a line extension application for new pharmaceutical forms that do not involve a new daily dose, the lack of additional clinical efficacy and safety data is acceptable.

IV.5 Clinical safety

Calcium plus vitamin D is contraindicated in patients with hypercalcaemia, hypercalciuria, hyperparathyroidism, nephrolithiasis, Zollinger-Ellison syndrome, hypervitaminosis D or hypersensitivity to any of the ingredients.

Adverse reactions of a generally mild nature have been observed with calcium carbonate treatment, especially constipation and flatulence. 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 arrhythmias 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 on severe hypercalcaemia under vitamin D/calcium treatment have occurred with doses of vitamin D exceeding 10.000 IU per day.

With respect to vitamin D, very large amounts over a long time 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.

Post marketing experience

Calcium carbonate and vitamin D was first licensed in 1960 and the estimated patient exposure is approximately 2.3 million patient days per year. PSUR reports for calcium 500 mg/vitamin D₃ 200 IU and calcium 500 mg/ vitamin D₃ 400 IU cover the period from the first launch on the market until 31 December 2001. In the latest PSUR, three serious unlisted reactions, in two patients, have been reported: one event each of hyperkalaemia, leukaemia and renal failure. There are no documented cases of acute overdose of the MAH's calcium/vitamin D medicinal products. The product information has not been updated specifically for this procedure but has been continuously updated through the years, e.g. to include advice on timing of calcium administration to avoid interactions described in the literature between calcium and certain other drugs.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfills the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The Applicant has provided a justification for not submitting a Risk Management Plan, declaring that the active substances of this product are widely used well-known substances that also are a normal part of the human diet. Vitamin D and calcium are used alone or in combination in medicinal products and dietary supplements since several decades. The combination was first licensed in 1960.

It is agreed that the safety profile of calcium/cholecalciferol can be considered as well established and that routine pharmacovigilance activities are sufficient to identify actual or potential risks with these products. Therefore a Risk Management Plan is not considered necessary.

Periodic Safety Update Report (PSUR)

The applicant has requested the PSUR cycle to be synchronized with the already approved Calcichew products as calcium carbonate + vitamin D₃ are a well known combination of active substances. The already approved Calcichew products are under evaluation in the

renewal procedure in Sweden at this point in time. The request is acceptable and the use of (not yet published) EU-HBD and related DLP are recommended.

IV.6 Discussion on the clinical aspects

Once-daily administration of calcium and vitamin D has in published clinical studies been shown to be equivalent to twice-daily administration for the total daily dose of 1000 mg calcium plus 800 IU vitamin D. Patient compliance with this regimen is expected to be at least as good as with the twice daily dosing.

Calcium plus vitamin D in a daily dose of 1000 mg calcium and 800 IU vitamin D is effective for prevention and treatment of vitamin D and calcium deficiency in the elderly. Vitamin D and calcium supplement is also effective in these doses as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. Clinical data support a once daily dosing of calcium and vitamin D.

Vitamin D and calcium are natural food components and have been administered as supplementation to natural intake for several decades. These medicinal products are well known. Risk of intoxication is not foreseen for the actual products with the recommended daily doses of 1000 mg calcium and 400 – 800 IU vitamin D. Once daily dosing is not considered to increase the risk of overdosing.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The SPC, PL and labelling are acceptable.

The risk/benefit ratio is considered positive and Calcichew-D3 1000 mg/800 IU chewable tablet and Calci-D3 500 mg/400 IU film-coated tablet are recommended for approval.

VI. APPROVAL

The decentralised procedure for Calcichew-D3 1000 mg/800 IU chewable tablet and Calci-D3 500 mg/400 IU film-coated tablet was successfully finalised on 4 June 2008.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
						Y/N (version)