LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Calcichew-D3 Melon, Calcichew-D3 Citron, Calcichew-D3 Melon (calcium carbonate/cholecalciferol)

SE/H/126/06-08/DC

This module reflects the scientific discussion for the approval of Calcichew-D3 Melon, Calcichew-D3 Citron. The procedure was finalised on 2015-05-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Takeda Nycomed AS has applied for a marketing authorisation for Calcichew-D3 Melon 500 mg/400 IU Chewable tablet, Calcichew-D3 Citron 500 mg/1000 IU Chewable tablet, Calcichew-D3 Melon 500 mg/1000 IU Chewable tablet. The active substance calcium and vitamin D3 (cholecalciferol) is the same as in Calcichew-D3 Citron 500 mg/400 IE, marketed by Takeda Nycomed AS since 1996.

For approved indications, see the Summary of Product Characteristics.

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

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of calcium and vitamin D are well-known and text-book knowledge. No new data have been presented that alter or give reason for re-evaluation of the non-clinical profile for these products. The dose levels are

within the dosage range commonly used in clinical practise and no additional non-clinical data is considered to be needed.

III.2 Ecotoxicity/environmental risk assessment

The product is intended to substitute for other products on the market and contains no components that result in additional hazard to the environment. In addition, considering the wide spread use of the drug substances, no significant increase in environmental exposure are anticipated. The justification for absence of environmental risk assessment is considered adequate.

III.3 Discussion on the non-clinical aspects

Products containing calcium and vitamin D have been available in the EU for more than 20 years and their use is well-established with recognised efficacy and acceptable safety. There have been no objections for approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcium carbonate and vitamin D, in combination, was first licensed in 1989. Calcium carbonate with cholecalciferol combination is used in the treatment of calcium and vitamin D deficiency. It is also used for supplementation of calcium and vitamin D as an adjunct to specific treatment of osteoporosis in patients who have combined deficiency of calcium and vitamin D or in patients with a high risk of such deficiency.

IV.2 Pharmacokinetics

No new pharmacokinetic studies have been conducted and none are needed for this extension application. The applied products have the same qualitative composition as the previously approved Calcichew-D3 Citron 500 mg/400 IE chewable tablets, and differ only in the flavour and/or amount of vitamin D3. The product is manufactured by the same manufacturer and process and the dissolution profiles are similar under identical conditions. In addition, the products are intended to be a complement to dietary calcium and vitamin D3, which might be highly variable.

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been conducted and none are needed for this extension application. The applied products have the same qualitative composition as the previously approved Calcichew-D3 Citron 500 mg/400 IE chewable tablets.

IV.4 Clinical efficacy

No new clinical studies have been conducted and none are needed for this extension application. The applied products have the same qualitative composition as the previously approved Calcichew-D3 Citron 500 mg/400 IE chewable tablets.
The efficacy of vitamin D and calcium supplement as an adjunct to osteoporosis treatment is well established in the proposed indications: *Prevention and treatment of vitamin D and calcium deficiency. Vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.* The fixed dose

combination may increase the adherence and compliance to the treatment. The main clinical studies have used dosages 400 IU or 800 IU of vitamin D.
The new strength of vitamin D in the proposed calcium and vitamin D combinations addressed in this application is up to 1000 IU.

In some review articles referred by the Applicant, the minimum desirable level serum 25(OH)D level has been reported approximately 75 nmol/l and an intake of 1000 IU/day of vitamin D was suggested to bringing the average individual's level to approximately 75 nmol/l. The proposed vitamin D concentration of up to 1000 IU may offer the potential to reach this level of serum 25(OH) D whilst remaining within acceptable upper limits, although the evidence supporting the efficacy of substitution with 1000IE compared to 800IE in clinical outcomes is considered limited.

IV.5 Clinical safety

The clinical safety of the combined tablets has been previously documented (Clinical Overview calcium/vitamin D 500 mg/200 IU or 400 IU, 2002, PSUR 14, 2013). Calcium and vitamin D supplementation is a well-established treatment within the current indication as a treatment for patients with vitamin D and calcium deficiency and as an adjunct to other osteoporosis treatment. Periodic Safety Update Reports (PSURs) cover the period from the first market launch until 31 October 2013.

Calcium plus vitamin D is contraindicated in patients with hypercalcaemia, hypercalciuria, severe renal impairment, nephrolithiasis, hypervitaminosis D or hypersensitivity to any of the ingredients (calcium carbonate and cholecalciferol SmPC). Adverse reactions of a generally mild nature have been observed with calcium carbonate treatment, and include constipation, flatulence, nausea and diarrhoea.

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 arrythmias may occur (European Commission, Health and Consumer Protection Directorate–General. 2003). 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 of severe hypercalcaemia during vitamin D/calcium treatment have occurred with doses of vitamin D exceeding 10,000 IU per day.

Considering vitamin D, very large amounts over a long 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.

The SmPC for calcium carbonate with cholecalciferol recommends that the product should not be used in patients with severe renal impairment (calcium carbonate and cholecalciferol SmPC). Calcium carbonate with cholecalciferol tablets should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D3 is not metabolised normally and other forms of vitamin D should be used.

In a Cochrane meta-analysis, hypercalcaemia was reported more often when vitamin D or its analogues were given compared with placebo or calcium, a small increase in gastrointestinal

symptoms were noted and a statistically significant increase in the incidence of renal calculi or renal insufficiency was also reported.

The safety of vitamin D and calcium supplement as an adjunct to osteoporosis treatment is well established. The vast majority of clinical studies have used dosages 400 IU or 800 IU of vitamin D. However, that calcium/vitamin D3 with a dose of 1,000 IU/day of Vitamin D3 has been approved and marketed in several European countries.

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of vitamin D. For adults, hypercalcaemia was selected as the indicator of toxicity. Taking into account uncertainties associated with the clinical studies, the upper limit for adults including pregnant and lactating women was set at 4,000 IU/day (EFSA The European Food Safety Authority Journal 2012;10(7):2813). The proposed dose of 1,000 IU Vitamin D3 is considered acceptable.

IV.6 Risk Management Plans

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 Calcichew-D3 Melon and Calcichew-D3 Citron.

Summary of safety concerns	
Important identified risks	Hypervitaminosis D
	Aggravation of diseases or conditions resulting in or from hypercalcaemia and/or hypercalciuria such as nephrolithiasis
	Interaction with cardiac glycosides
Important potential risks	In patients suffering from sarcoidosis there is a risk of increased metabolism of vitamin D to its active form
Missing information	None

Routine pharmacovigilance is proposed for all safety concerns.

The RMP needs to be updated according to the outcome of this procedure regarding the proposed new strenght.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Calcichew D3 500mg/400IE, SE/H/126/01/1B/56. The bridging report submitted by the applicant has been found acceptable.>

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Calcichew-D3 Melon 500 mg/400 IU Chewable tablet, Calcichew-D3 Citron 500 mg/1000 IU Chewable tablet, Calcichew-D3 Melon 500 mg/1000 IU Chewable tablet is recommended for approval.

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Calcichew-D3 Melon 500 mg/400 IU Chewable tablet, Calcichew-D3 Citron 500 mg/1000 IU Chewable tablet, Calcichew-D3 Melon 500 mg/1000 IU Chewable tablet was positively finalised on 2015-05-20.

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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)

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