PUBLIC ASSESSMENT REPORT
Scientific Discussion

CALTRATE VITAMIN D₃ 600 mg/400 IU,
film-coated tablet
Calcium/Vitamin D₃

FR/H/320/01/MR

Applicant: Wyeth Pharmaceuticals France

Date of the PAR: September 2009
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1. **INTRODUCTION**

Based on the review of the quality, safety and efficacy data, Afssaps has granted a marketing authorisation for CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablet (calcium/vitamin D₃) from Wyeth Pharmaceuticals France in the:

- correction of combined vitamin D and calcium deficiencies in the elderly;
- and supply of vitamin D and calcium as an adjunct to specific treatments for osteoporosis, in patients where combined vitamin D and calcium deficiencies have been diagnosed or those at high risk of such deficiency.

A comprehensive description of indications and doses is given in the SPC.

This application is based on Article 10a of Directive 2001/83/EC as amended, since calcium and vitamin D are well-established use drugs in the claimed indications, both as associations or fixed combinations.

With France acting as the Reference Member State in this Mutual Recognition Procedure, the Applicant is applying for the Marketing Authorisations of CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablets in Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, Spain, Ireland, Italy, Netherlands, Portugal and Slovak Republic.

CALTRATE VITAMIN D₃ 600 mg/400 IU is presented in the form of film-coated tablets containing 600 mg of calcium (as calcium carbonate) and 400 IU (10 microgram) of cholecalciferol. The excipients are microcrystalline cellulose, povidone, crospovidone type A, sodium laurilsulphate, sodium croscarmellose, magnesium stearate, DL-α-tocopherol, partially hydrogenated soya bean oil, sucrose, bovine gelatin, corn starch, Opadry beige, light liquid paraffin and talc.

No new preclinical and clinical studies were conducted, which is acceptable for this kind of application.

The clinical pharmacology, efficacy and safety of calcium/vitamin D₃ have already been extensively studied and characterized during the development of the several drug products already marketed.

During the procedure, no potential serious risk to public health was raised.
2. QUALITY ASPECTS

2.1 Introduction

The medicinal product CALTRATE VITAMIN D₃ 600 mg/400 IU is a grey/beige, capsule-shaped, film-coated tablet. One side is scored and engraved with “D” on the left and “600” on the right of the score. The other side is engraved with “Caltrate.”

It contains calcium carbonate equivalent to 600 mg of calcium base, and cholecalciferol concentrate (Dry Vitamin D₃) corresponding to 400 IU of vitamin D₃.

The formulation comprises the following excipients: microcrystalline cellulose, povidone, crospovidone type A, sodium laurilsulphate, magnesium stearate, DL-alpha-tocopherol, partially hydrogenated soya bean oil, sucrose, bovine gelatine and corn starch within the uncoated tablet, and Opadry beige, light liquid paraffin and talc within the film-coating. The product is packaged in opaque white HDPE bottles closed with a polypropylene cap with an induction innerseal.

2.2 Drug substance

Two active substances (calcium carbonate and cholecalciferol or Vitamin D₃) are used in the drug product.

Calcium carbonate is described in the Ph. Eur. and the manufacturer holds a Certificate of Suitability of the monograph.

Calcium carbonate is a white or almost white powder which is practically insoluble in water. The specifications of calcium carbonate conform to the Ph. Eur. monograph with additional limit for residual solvent.

Stability results submitted are sufficient to confirm the proposed re-test period.

Cholecalciferol is described in the Ph. Eur. and the manufacturer holds a certificate of suitability of the monograph. The specifications of cholecalciferol conform to the Ph. Eur. with additional limits for related substances and residual solvents.

Cholecalciferol is supplied as a pre-formulated concentrate which meets the requirements of the current Ph. Eur. monograph for Cholecalciferol Concentrate – Powder Form. The proposed re-test period is supported by submitted stability results.

2.3 Medicinal product

The medicinal product CALTRATE VITAMIN D₃ 600 mg/400 IU film-coated tablet is formulated using excipients described in the Ph. Eur. All raw materials used in the product have 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 (EMEA/410/01). The development is sufficiently documented in accordance with the relevant European guidelines. The manufacturing process is satisfactorily described. The main operating parameters are clearly set. The type of equipment is defined. Critical steps have been identified. A manufacturing flow-chart highlighting the different steps and in process controls is provided. The manufacturing process is adequately validated at industrial-scale at the declared manufacturing site.

Excipients comply with the Ph. Eur. monograph with exception of the coating ingredient (Opadry Beige) which has in house specifications.

Magnesium stearate used in the manufacture of the drug product is obtained from a vegetable source.

The product specifications cover appropriate parameters for this dosage form.
The analytical methods used are satisfactorily described and validated. Certificates of analysis are provided for four commercial batches manufactured in the declared manufacturing site. The batch results show that the finished product meet the specifications set. The specifications comply with the Ph. Eur. requirements for tablets at time of registration and to the ICH recommendations. The justification of the specifications is acceptable. Three volumes of bottles made in white opaque HDPE are proposed for the various counts of tablets and sealed with an adapted white polypropylene screw cap with an induction inner seal. This packaging has already been commercially used for a number of years. However, the suitability of the packaging has been verified on drug product stability studies. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Stability data provided under ICH conditions support the shelf life claimed in the SPC, 24 months with storage condition “Store below 25° C”.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Regarding the preclinical aspects, no additional non clinical studies were performed. In accordance to Directive 2001/83/EC as amended, adequate scientific literature has been provided: 10 bibliographical references related to non-clinical tests have been submitted. A favourable opinion is given on the preclinical part of the dossier.

Environmental risk
As calcium and vitamin D₃ are well-known substances, such an evaluation of the potential environmental risk is deemed unnecessary.

4. CLINICAL ASPECTS

4.1 Introduction

CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablet is intended for correction of combined vitamin D and calcium deficiencies in the elderly and supply of vitamin D and calcium as an adjunct to specific treatments for osteoporosis, in patients where combined vitamin D and calcium deficiencies have been diagnosed or those at high risk of such deficiency. CALTRATE VITAMIN D₃ 600 mg/400 IU is intended for twice daily administration (one tablet in the morning and one tablet in the evening).

Calcium and Vitamin D₃ are well-known active substances with established efficacy and tolerability.

4.2 Pharmacokinetics

No new pharmacokinetic data have been submitted. It was not necessary because CALTRATE VITAMIN D₃ 600 mg/400 IU has the same qualitative and quantitative composition of active substances as other products previously approved. CALTRATE VITAMIN D₃ 600 mg/400 IU is a medicinal product with well-known excipients.
### 4.3 Discussion on the clinical aspects

No new clinical studies were conducted, which is considered acceptable given that the application was based on a well-established use. A clinical overview on the clinical pharmacology, efficacy and safety of the active ingredients (with corresponding references from the literature) is provided.

CALTRATE VITAMIN D₃ 600 mg/400 IU was approved in France in 1995, and therefore with more than 10 years of experience.

In this context, a bibliographical application is considered adequate, due to the wide safety margin of calcium and vitamin D₃ and its well-established use. The MAH has provided adequate scientific literature: 39 publications have been submitted.

**Efficacy** profile of calcium and vitamin D₃ is already well-established and documented.

The provided bibliographical data have shown the efficacy of calcium-vitamin D supplementation on calcium and vitamin D deficiency in elderly patients of both genders. Changes were observed after 6 months of treatment at daily doses of 1.0 to 1.2 g of calcium and 700 to 800 IU of vitamin D.

This supplementation appears beneficial in the prevention of osteoporotic fractures in patients where combined vitamin D and calcium deficiency.

CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablets is a well accepted formulation which combines optimal doses of calcium and vitamin D₃.

The proposed posology (two tablets per day) corresponds to the established regimen adopted throughout the literature in the requested indications.

The RMS has reviewed the safety profile of CALTRATE VITAMIN D₃ and was of the opinion that, even if the risk-benefit ratio remains favourable, a warning should be added in the product information in order to minimise the risk of tablet choking. Indeed, a PSUR for the period from 31 May 2001 to 22 May 2006 has been submitted by the MAH. During this period, there have been 39 adverse drug reaction reports, of which 8 were serious and 31 were non-serious. One fatal case was reported: the patient choked on one tablet of calcium/vitamin D and asphyxiated. A cumulative review of the safety surveillance system database was conducted for other reports of fatal asphyxiation coincident with calcium carbonate/vitamin D use. Even though the risk of choking is low, the RMS was of the opinion that the following warning should be added in section 4.4 of the SPC and in the PIL, in order to minimise any risk of choking:

> “Post-marketing cases of asphyxiation due to tablet choking have been reported. It is always recommended to take tablets with a large glass of water (200 ml). In order to facilitate intake by patients, especially elderly or patients with known difficulties in swallowing, the breakable tablet may be divided into two parts before taking them with a large glass of water.”

This proposition was accepted by the CMSs.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC.

The PSUR cycle will be modified as follows: 6-monthly PSUR should be submitted during 2 years from the date of February 24th 2009. Next renewal will be on May 1st, 2014.
For future PSUR, the company should closely monitor, document and analyse:
- all serious cases in a special section (CIOMS forms should also be provided),
- allergic reactions including hypersensitivity, swelling face and eyelid edema,
- nephrolitiasis

No description of the Risk Management System has been provided since the application based on well-established use.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils 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. However, the applicant should give a description of the back-up procedure in place, should indicate whether the following items (back-up procedure, meeting commitments, archiving,...) are covered by written procedures, more details about arrangements established with business partners are requested, should give reassurance that he training include also staff who may receive or process to safety reports.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The Marketing Authorisation Holder applied for the registration of CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablet in accordance with the article 10a “well-established use” of Directive 2001/83/EC.

Satisfactory chemical-pharmaceutical documentation of CALTRATE VITAMIN D₃ 600 mg/400 IU has been provided, assuring consistent and sufficient quality of the product.

No new preclinical and clinical studies were conducted, which is acceptable for this kind of application.

The clinical pharmacology, efficacy and safety of calcium/vitamin D₃ have already been extensively studied and characterized during the development of the several drug products already marketed.

No potential serious risk to public health was raised during the procedure.

The SPC, Package Leaflet (PL) and packaging are in the agreed template.

User testing of the package leaflet has been performed.

Comments from CMSs have been received and taken into account. Finally, agreement between Member States was reached during procedure. There was no further discussion at the CMD(h).

The mutual recognition procedure for CALTRATE VITAMIN D₃ 600 mg/400 IU, film-coated tablet was successfully finalised on 24 February 2009.