CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

CaD 500/880 orange, effervescent granules Will Pharma B.V., the Netherlands

calcium carbonate and cholecalciferol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 108608

26 February 2013

Pharmacotherapeutic group:	calcium, combinations with vitamin D
ATC code:	A11CC05/A12AX/A11CC20
Route of administration:	oral
Therapeutic indication:	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.
Prescription status:	prescription only
Date of authorisation in NL:	12 October 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for CaD 500/880 orange, effervescent granules from Will Pharma B.V. The date of authorisation was on 12 October 2011 in the Netherlands.

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 SPC.

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 D3 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 D3 administration corrects secondary senile hyperparathyroidism by counteracting the increase in parathyroid hormone (PTH) which is caused by calcium and vitamin D3 deficiency and which causes increased bone resorption.

This national procedure concerns a line extension to the registered product CaD 500/440 citroen, effervescent granules (NL License RVG 18866), which has been registered since 10 June 1997. The differences with the original product are the new strength for cholecalciferol and the flavour. Also, CaD 1000/880 citroen, effervescent granules (NL RVG 18867) has been registered since 1997.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of for CaD 500/880 orange, effervescent granules.This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant 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 applicant 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.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required in view of the therapeutic indications.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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 anorganic 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 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 European Pharmacopoeia.

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 active substances are controlled with the tests and requirements of their Ph.Eur. monographs and the tests and requirements described in the Certificates of Suitability. Batch analytical data demonstrating compliance with these specifications have been provided for two batches of calcium carbonate and three batches of cholecalciferol.
Cholecalciferol is used in the manufacturing process of the drug product as concentrate powder. Sufficient information on this intermediate product has been provided.

Stability of drug substance
For calcium carbonate it has been confirmed that testing on compliance with its specification will be performed immediately prior to manufacture of the drug product.
Stability data on the active substance cholecaliferol concentrate have been provided for three full-scale batches stored at 15°C, 25°C/60% RH (24 months) and 40°C/75% RH (6 months). No trends or out of specification results were observed during the stability studies.
The active substance is stable for 24 months with the storage condition “Store in the unopened original container and at a temperature below 15°C, keep the container tightly closed.”

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
CaD 500/880 orange contains per sachet 1250 mg calcium carbonate, corresponding to 500 mg calcium, and cholecalciferol concentrate powder corresponding to 880 IE. The product is an effervescent granulate with white to off-white effervescent granules, divided in sachets.

Excipients are citric acid anhydrous (E330), mannitol (E421), orange flavour, saccharin sodium (E954), modified starch and sucrose.
The effervescent granulate is packed in paper/polyethylene/aluminium/polyethylene sachets.

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 product are bio-equivalent and no further bioequivalence studies are required. No overages of the active substances calcium and cholecalciferol have been added to the formulation.

Manufacturing process
A non standard manufacturing process has been employed based on the amount of cholecalciferol in the final drug product. The whole process consists of three main steps: granulation, blending and packaging.
The manufacturing process has been validated on three pilot-scale batches and one full-scale batch. The manufacturing process is considered validated.

Control of excipients
Almost all of the excipients comply with the Ph.Eur. These specifications are acceptable. The orange flavour has in-house specifications. The specification is acceptable and is in compliance with the EU legislation.

Quality control of drug product
The product specification includes tests for appearance of granules, solution and sachets, pH of the solution, residual humidity, disintegration time, average mass, uniformity of dosage units, identification of calcium and cholecalciferol, degradation products and microbiological characteristics.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (6 months) and 30°/65% 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
At accelerated conditions out of specification results were observed for the degradation products. At long term and intermediate conditions no changes were observed.
The claimed shelf-life of 18 months when stored in paper/PE/Al/PE sachets with the storage condition ‘store below 30°C’ was granted. Post approval the shelf life was extended to 24 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lanolin is used in the manufacturing of the drug product. Lanolin is of animal origin. It is derived from the wool of healthy sheep. Lanolin complies with Ph.Eur. monograph 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”.

II.2 Non-clinical aspects

The product is a line extension to CaD 500/440 citroen, which is available on the European market. 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.

Environmental risk assessment

The approval of this product is unlikely to result in a significant increase in the environmental exposure to cholecalciferol and calcium carbonate, because both substances are widely present in food supplements. The lack of additional environment studies is therefore justified.

II.3 Clinical aspects

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 Board agreed that no further clinical studies are required.

The use of calcium vitamin D combination for the treatment of the combined calcium and vitamin D deficiency or as adjunct to specific therapy for osteoporosis is well established and incorporated in virtually all guidance on calcium vitamin D deficiency and osteoporosis (for example EFSA and the CBO guidelines 2010).

The rationale for the development of the 500 mg calcium and 880 I.U. vitamin D3 formulation is based on the evidence that many elderly patients only receive a suboptimal proportion of the recommended daily amount of calcium from dietary sources (EFSA and the CBO guidelines 2010). Since the average daily dietary calcium intake in the Netherlands is around 700 mg per day, supplementation of 500 mg per day is adequate in the majority of patients. However, new recent insights show that a large proportion of osteoporotic patients have a vitamin D deficiency. Vitamin D deficiency is associated with impaired bone strength and an increased risk of falling.

This new strength of the medicinal product CaD is targeting mainly a population presenting a suboptimal calcium intake with a clinically relevant inadequate vitamin D status. A once-daily supplementation of a fraction of the calcium requirement together with vitamin D will allows these patients to receive the recommended daily amount of calcium and vitamin D.

Calcium carbonate and vitamin D3 have been used in the Community for decades. The active substances of CaD 500/880 are identical to CaD 500/440 (calcium 500 mg/vitamin D3 440 IU) and CaD 1000/880 (calcium 1000 mg/vitamin D3 880 IU), which have been marketed in the Netherlands since 1997. These products are effective and safe; periodic reports of pharmacovigilance indicate that combination therapy with effervescent granules of calcium carbonate and vitamin D3 is well tolerated with no clinically relevant adverse events.

Risk management plan

The application concerns a medicinal product with more than 10 years post-authorisation clinical experience. The safety profiles of calcium carbonate and cholecalciferol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal products. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for the already approved product CaD 500/440 citroen, effervescent granules.

Readability test

The package leaflet 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 with 4 participants, followed by two rounds with 10 participants each. The questions covered sufficiently the following areas: traceability, comprehensibility and applicability. There were no changes made to the PIL based on

preliminary testing, the first or the second round. The results of the test indicate that the PIL is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable and patients/users are able to act upon the information that it contains. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

CaD 500/880 orange, effervescent granules has a proven chemical-pharmaceutical quality and is a legitimate line extension to CaD 500/440 citroen, effervescent granules. Well-established use has been sufficiently substantiated based on literature.

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 is waived according to the Guideline on the investigation of bioequivalence.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other calcium carbonate and cholecalciferol containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated with the reference product, and has therefore granted a marketing authorisation. CaD 500/880 orange, effervescent granules was authorised in the Netherlands on 12 October 2011.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to perform stability studies on the first three industrial-scale batches manufactured post approval under ICH stability conditions. This commitment has been fulfilled.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CBO	Centraal Begeleidingsorgaan (Central Accompaniment Organization)
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EFSA	European Food Safety Authority
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the shelf life or storage conditions of the finished product; extension of the shelf life to 24 months.	--	IB	21-2-2012	16-4-2012	Approval	N
Submission of stability results on 3 industrial batches.	--	Post-approval commitment	2-4-2012	7-5-2012	Approval	N