PUBLIC ASSESSMENT REPORT

Decentralised Procedure

DE/H/2858/001/DC

Calcium 1000 mg / Vitamin D3 880 I.U. chewable tablets

Calcium carbonate, Cholecalciferol

Marketing authorisation holder:

Hexal Aktiengesellschaft

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Calcium Vitamin D3 HAM 1000mg/880 I.E., Kautabletten
INN (or common name) of the active substance(s):	calcium carbonate, Colecalciferol
Pharmaco-therapeutic group (ATC Code):	A12AX
Pharmaceutical form(s) and strength(s):	Chewable tablet – Calcium 1000 mg / 880 I.U.Vitamin D3
Reference Number for the Procedure:	DE/H/2858/001
Reference Member State:	DE
Member States concerned:	BE, ES, FR, IT, LU, NL
Applicant (name and address)	Hexal Aktiengesellschaft Industriestr. 25 83607 Holzkirchen
Names and addresses of manufacturers of dosage form	Hermes Arzneimittel GmbH Georg-Kalb-Str. 5-8 82049 Großhesselohe Deutschland Hermes Arzneimittel GmbH (BS 1) Hans-Urmiller-Ring 52 82515 Wolfratshausen Deutschland
Names and addresses of manufacturers responsible for batch release in the EEA	Salutas Pharma GmbH Otto-von-Guericke-Allee 1 39179 Barleben Deutschland

List of abbreviations

API	Active pharmaceutical ingredient
BAN	British Approved Names
BP	British Pharmacopoeia
CFU	Colony forming unit
DAB	German Pharmacopoeia (Deutsches Arzneibuch)
DAC	German Pharmaceutical Codex a Supplementary Pharmacopoeia to the European and German Pharmacopoeia (Deutscher Arzneimittel-Codex)
EgB6	Supplement to the German Pharmacopoeia 6 (Ergänzungsband zum DAB 6)
HELV	Swiss Pharmacopoeia (Pharmacopoeia Helvetia)
LOD	Loss of drying
Mn	Number average molecular weight
Mw	Weight average molecular weight
NfG	Note for Guidance
NLT	Not less than
NMT	Not more than
O.d.s.	On dry substance
ÖAB	Austrian Pharmacopoeia (Österreichisches Arzneibuch)
Ph.Eur.	European Pharmacopoeia (EP)
USP	United States Pharmacopoeia

1 INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Calcium-D3 chewable tablets, for the 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, **is approvable** provided that the applicant commits to perform post authorisation follow-up measures.

2 EXECUTIVE SUMMARY

2.1 Problem statement

Osteoporosis (OP) is an established and well-defined disease that affects more than 75 million people in Europe, Japan and the USA, and causes more than 2.3 million fractures annually in Europe and the USA alone. The lifetime risk for hip, vertebral and forearm (wrist) fractures has been estimated to be approximately 40%, similar to that for coronary heart disease. Osteoporosis does not only cause fractures, it also causes people to become bedridden with secondary complications that may be life threatening in the elderly. Since osteoporosis also causes back pain and loss of height, prevention of the disease and its associated fractures is essential for maintaining health, quality of life, and independence among the elderly (0310). Osteoporosis is a systemic skeletal disease characterised by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility. Early osteoporosis is not usually diagnosed and remains asymptomatic; it does not become clinically evident until fractures occur. Loss of bone density occurs with advancing age and rates of fracture increase markedly with age, giving rise to significant morbidity and some mortality.

2.2 About the product

Calcium and vitamin D supplementation is the well established basis of osteoporosis therapy. Women who are oestrogen-deprived require an average oral intake of 1,500 mg/d of elemental calcium to remain in calcium equilibrium. In order to increase calcium utilisation, vitamin D preparations have been used in osteoporosis, as calcium absorption is impaired and serum levels of the active metabolite, 1,25-dihydroxy-vitamin D, are marginally low.
Supplementation of calcium and vitamin D as a supportive treatment in primary and secondary osteoporosis is recommended by several internationally acknowledged organisations.

2.3 General comments on the submitted dossier

The applicant has filed an application for Marketing Authorisation according to Article 10(a) of Directive 2001/83/EC, as amended, for Calcium- D3 chewable tablets used to achieve a daily dose of 1.000 mg calcium and 22 µg cholecalciferol (corresponding to 880 IU). Accordingly, this application refers to published scientific literature. This is reasonable and justified, since the active ingredients of the medicinal product, i.e. calcium and vitamin D3, are generally established for medicinal use and are acknowledged as being both efficient and possessing an acceptable level of safety and since comprehensive information exists on their biochemistry, pharmacology and clinical use. This can be derived from the fact that a variety of products containing calcium and/or vitamin D3 are marketed in numerous countries both in and outside Europe and have proved to be safe and effective for many decades.

2.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

No new clinical studies have been performed by the Applicant. Instead bibliographical data are submitted. The Applicant does not provide information with respect to GLP compliance. However the selected references exhibit an adequate scientific standard for this type of medicinal product.

3 SCIENTIFIC OVERVIEW AND DISCUSSION

3.1 Quality aspects

Drug substance:
The dossier complies with relevant EU guidelines and Directives.

Drug substance
Two drug substances are included in the chewable tablets; calcium carbonate and Cholecalciferol (vitamin D3) as Cholecalciferol concentrate (powder form).

Calcium carbonate:
Calcium carbonate is manufactured by two alternative manufacturers and is covered by European Certificates of Suitability. The copies of which are presented in the documentation.
An appropriate specification is provided for the active substance Calcium carbonate.
The active substance is controlled according to the requirements of the Ph. Eur. monograph and additional parameters as specified in granted CEPs.

Calcium carbonate: The proposed retest periods are justified.

Cholecalciferol:
Cholecalciferol from two alternative suppliers have received CEPs. The CEPs certify that this drug substance is suitably controlled by the current version of the monograph on cholecalciferol of the Ph. Eur.. Further testing parameters are provided on the respective CEPs.

Cholecalciferol concentrate (powder form):
Cholecalciferol concentrate (powder form) has received an ASMF. The ASMF of Cholecalciferol concentrate (powder form) has been accepted (RMS = DE).

The control tests and specifications for drug substances product are adequately drawn up.

Stability studies have been performed with the drug substance.

a) Data of Cholecalciferol concentrate (powder form) manufacturer:
The proposed re-test period is justified.
b) Data of the drug product manufacturer Hermes:
The proposed re-test period is justified.

Drug Product
The drug product is a round, white tablet with surface and a breakmark, chewable tablet (1000 mg calcium and 880 IU vitamin D_3) .
The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The applicant commits to validate the first commercial batches.

The finished product specification is satisfactory. The methods have been described and adequately validated.

The conditions used in the stability studies are according to the ICH stability guideline.
Two kinds of stability studies are provided for "Calcium Vitamin D3 1000/880". One where the tablets are stored in the Polypropylene tubes with polyethylene desiccant stoppers and one where the tablets are stored in laminated aluminium – paper-foil.
The tested parameters during shelf-life are considered sufficient. The methods used during the stability studies are the same as presented for release.

A forced degradation study on the finished product has been carried out.

Additionally, for stability studies the packaging material as proposed for marketing was used and is described in Module 3.2.P.7 . The stability testing was performed according to the "Note for Guidance on Stability Testing: Stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1 corr.)".

Approved shelf-life:
Polypropylene tubes with polyethylene desiccant stoppers: 24 months with the storage precautions Keep the tablet container tightly closed in order to protect from moisture."

Laminated aluminium-paper-foil: 24 months with no storage precaution.

In-use stability studies carried out according to Note for Guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99). The proposed shelf-life of 24 months is justified.

Photostability studies in accordance with "Note for Guidance on the Photostability testing of New Active Substances and Medical products (CPMP/ICH/279/95) have been provided.

The quality documentation is found sufficient; therefore the marketing authorisation has been granted.

3.2 Nonclinical aspects

No new non-clinical studies have been performed by the Applicant. The two active ingredients in the fixed combination of their respective amounts are widely used in the medical practice in Europe. The pharmacology, pharmacokinetic and toxicology is well known and exhibit an established safety profile. From the non-clinical point of view there are no objections against marketing authorisation. The non-clinical parts of the SmPC and the PIL have been amended according to the member states comments.

3.3 Clinical aspects

No new clinical studies have been performed by the applicant. The two active ingredients in the fixed combination of their respective amounts are widely used in the medical practice in Europe. From the clinical point of view there are no objections against a marketing authorisation. The clinical parts of the SmPC and the PIL have been amended according to the member states comments.

4 BENEFIT RISK ASSESSMENT

Overall the bibliographic data demonstrate a well known positive benefit risk ratio.