CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Phosphosorb 660 mg, film-coated tablets
Fresenius Medical Care Deutschland GmbH, Germany

calcium acetate

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/0887/01/MR
Registration number in the Netherlands: RVG 32250

Date of first publication: 18 May 2009
Last revision: 23 August 2011

Pharmacotherapeutic group:	mineral supplements, calcium
ATC code:	A12AA12
Route of administration:	oral
Therapeutic indication:	hyperphosphataemia in patients with chronic renal insufficiency undergoing dialysis.
Prescription status:	prescription only, except for CY, DE, and LU where the prescription status is pharmacy only
Date of authorisation in NL:	11 July 2006
Concerned Member States:	Mutual recognition procedure with AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, SE, SI, SK and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(a) well-established use application.

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 member states have granted a marketing authorisation for Phosphosorb 660 mg, film-coated tablets from Fresenius Medical Care Deutschland GmbH, Germany. The date of authorisation was on 11 July 2006 in the Netherlands. The product is indicated for the treatment of hyperphosphataemia in patients with chronic renal insufficiency undergoing dialysis.

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

Phosphosorb 660 mg contains calcium acetate, and is primarily intended in patients with chronic renal failure. They cannot excrete phosphate via the kidneys to the normal degree, and this leads to hyperphosphataemia. If dietary restriction is insufficient phosphate-binding substances must be used to reduce phosphate absorption in the gastro-intestinal tract. Calcium acetate taken with meals forms together with phosphate in the food poorly soluble calcium phosphate, which is excreted with faeces. Note that the calcium ions are not absorbed into the circulation.

The marketing authorisation is granted based on article 10(a) of Directive 2001/83/EC. This application concerns a bibliographical application based on well-established medicinal use of calcium acetate. 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.
The bibliographical information describes well-established use in the EU since 1991. Furthermore, there is no original/reference medicinal product to which essential similarity can be claimed for a generic application.

No scientific advice has been given to the MAH with respect to this product.

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 these product types 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 substance
Calcium acetate is described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white hygroscopic powder. It is freely soluble in water and slightly soluble in ethanol (96%). There are no stereochemistry or polymorphism issues.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active

substance. Competent Authorities/ EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The synthesis of the calcium acetate has been adequately described. Sufficient details have been provided. The drug substance has been adequately characterised.

Quality control of active substance
The drug substance specification complies with the Ph.Eur. monograph of sodium acetate, with additional requirements for particle size. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of active substance
Stability data have been obtained during storage at 25°C/60% RH (up to 49 months). The drug substance was packaged in the commercial packaging, i.e. HDPE bags in fibre board drums. The substance is stable at this condition. Based on the stability data provided, the claimed retest period of 36 months, with storage below 30 °C, has been granted.

** 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.*

Drug product
The product is formulated as a film-coated, direct-release tablet. The tablets are packaged into white HDPE jars (150 ml, 250 ml and 300 ml) with white LDPE caps. Each tablet contains 660.0 mg of the active ingredient calcium acetate. The tablets are white to yellowish oblong tablets with a breaking notch. The breaking notch is for facilitating swallowing only, not to divide the tablets into equal halves. Once the film coating is broken, the hygroscopicity of the active substance may lead to softening or other changes in the half tablets. No tests on this have been done. Tablets should not be broken "in advance" which is mentioned in the SPC.
The excipients are sucrose, gelatine, croscarmellose sodium, magnesium stearate, refined castor oil, saccharin sodium, and hypromellose.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of tablets. The packaging materials are usual and suitable for the product at issue.

Manufacture of the product
The tablets are prepared from a granulate, compressed and film-coated. The manufacturing process has been described sufficiently. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented for two batches (50% of the full scale batch size) in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Quality control of drug product
The product specification for the tablets includes tests for appearance, dimensions, identification, average mass, uniformity of mass (whole tablets), disintegration time, dissolution rate, resistance to crushing, loss on drying, tightness of container, assay and microbiological requirements. The MAH proposes a specific *in-vitro* dissolution profile for his product: not less than 80% will dissolve in 45 minutes to assure adequate *in-vivo* efficacy. A clinical justification for the dissolution limits is given by the MAH, based on the time that is available before food phosphates are absorbed from the gastro-intestinal tract into the blood stream. The proposed tests and requirements are acceptable. Satisfactory validation data for the analytical methods has been provided. Batch analysis data have been provided on three commercial batches. Compliance with the release requirements has been demonstrated.

Stability of the product
The tablets have been stored at 25°C/60% RH (up to 36 months), 30°C/65% RH (up to 12 months) and 40 °C/75% RH (up to 6 months). An increase in disintegration time and some fluctuation in dissolution rate have been observed at long-term storage conditions (36 months), leading to out of specification results. A shelf-life of 2 years, with an in-use period of 5 weeks after first opening of the bottles, can be granted. The storage condition is “Store below 30°C”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

Non-clinical data on calcium acetate are very limited. Pharmaco-toxicological properties are considered well-established in humans.
The submitted non-clinical overview is of sufficient quality. The overview covered the limited non-clinical issues relevant for pharmaco-toxicological assessment of the product, i.e. pharmacodynamics, pharmacokinetics, and toxicity (acute and repeated-dose toxicity, reproductive toxicity, genotoxic/carcinogenic potential) of calcium acetate.

Environmental risk assessment
As the active substance calcium acetate is a well-known substance and has been in well-established medicinal use for over ten years, the Environmental Risk Assessment is ended without testing requirements, in accordance with Article 10a of Directive 2001/83 as amended.

II.3 Clinical aspects

Pharmacokinetics
Calcium acetate is a phosphate binder, which primarily binds dietary phosphate in the stomach sparing the kidneys.
Neither bioequivalence nor bioavailability studies are necessary as calcium acetate exerts its pharmacological mechanism before absorption. The MAH provided a sufficient clinical overview discussing the pharmacokinetics of calcium acetate. No additional *in vitro* calcium or phosphorus absorption studies were submitted. However, this is not considered of major importance as sufficient information is available in the literature. A clinical justification for the dissolution specification of the tablets is given in the Clinical Overview, based on the time that is available before food phosphates are absorbed from the gastro-intestinal tract into the blood stream.

Pharmacodynamics
The active substance calcium acetate works by binding dietary phosphates in the gastro-intestinal tract, preventing them from being absorbed into the circulation. When calcium acetate is taken with meals, calcium forms together with phosphate in food the poorly soluble calcium phosphate, which is excreted with faeces. Also, to a lesser extent endogenous phosphate in the intestinal tract is bound by calcium acetate before (re-)absorption.

Clinical efficacy
Calcium acetate has long been in use as a phosphate binder in patients with dialysis-dependent renal failure. Nineteen clinical studies investigating the efficacy of calcium acetate as a phosphate binder have been summarized and tabulated in the submitted clinical overview. In these trials, efficacy was measured as the ability to reduce serum phosphate, normalize serum Ca x P product, suppress parathyroid hormone (PTH) and/or correct metabolic acidosis in renal failure.
The studies were mostly conducted in patients with chronic, dialysis-dependent renal failure for treatment periods of 4 – 52 weeks. Other studies were conducted in compensated renal failure. The studies proved calcium acetate to be an effective phosphate binder. When compared to calcium carbonate, calcium

acetate was demonstrated to be at least as equipotent and in some studies even superior. The mean dosage used in these studies ranged from 0.6 – 1.5 g/d calcium, equivalent to 2.38 – 5.95 g/d calcium acetate. This calcium dose is 40 -50 % lower than that used for calcium carbonate. The data obtained thus suggest a better phosphate binder capacity per mol of calcium delivered. This was explained by the better solubility of calcium acetate at pH levels of > 5.5 which makes this preparation suitable for patients with gastric hypoacidity.
Despite the tendency towards higher serum calcium on calcium acetate treatment in a number of studies, the Ca x P was reduced at least equally well as with calcium carbonate in the majority of studies and was even lower in one study.
PTH was proved to be regulated under calcium acetate as much as under calcium carbonate treatment, with one study proving even better reduction under the former.
Calcium acetate was also shown to be equally effective as calcium carbonate in the correction of metabolic acidosis.

Special populations
In one clinical study, the use of calcium acetate was evaluated in paediatric and adolescent patients with dialysis-dependent renal failure. Although calcium acetate was able to achieve relatively good control of serum phosphate, no sufficient information is available on the relationship of age to the effects of calcium acetate in paediatric patients.
The general dose recommendations given in the SPC for Phosphosorb corresponds to the therapeutic practice described for other calcium acetate products.
No clinical studies have been performed to investigate the use of calcium acetate during pregnancy and lactation.

Clinical safety
Calcium-containing phosphate binders are usually well tolerated. The adverse events essentially concern the overdose of calcium. Accordingly, the risk of adverse events depends on the absorbed fraction of calcium and its bioavailability. The observed side effects when calcium is used as a phosphate binder included: gastro-intestinal tract adverse events, acute/chronic elevations of calcium, elevation of Ca x P with consecutive soft tissue calcifications and development of adynamic osteopathy.
The incidence of gastrointestinal side effects such as nausea, vomiting, a sensation of bloating and eructation reported with calcium acetate was higher in some clinical studies than reported with calcium carbonate. The pharmaceutical formulation appears to have a major role. Studies with simple pharmaceutical preparations showed a higher side effect rate, while sugar-coated tables are usually associated with a tolerance level similar to that of calcium carbonate.
The development of hypercalcemia in patients taking calcium acetate is dependent on many factors; e.g., the calcium eliminating capacity of the extracorporeal techniques, the remodelling activity of the bone and the phosphorous content of the meal. Accordingly, the incidence of hypercalcemia is rated very differently in the clinical studies. Whereas in some studies, no episodes of hypercalcemia were observed, in others the hypercalcemia rate ranged from 5 – 28 %. However, in most cases the hypercalcemia followed a mild and asymptomatic course. In general, serum calcium must be regularly monitored and the calcium acetate dose accordingly adjusted. Patients should be warned about symptoms of hypercalcemia e.g. lethargy, anorexia, nausea, vomiting, psychotic symptoms, cardiac rhythm disorders or a rise in blood pressure.
The recommended upper limit of Ca x P product is cited as <4.5 $mmol^2/l^2$ (not to exceed 5.25 $mmol^2/l^2$) which will possibly reduce the risk of soft tissue calcification.

Post marketing experience
There have been no additional reports of adverse events related to the use of two comparable calcium acetate products (Phosphosorb® 475 mg and Phosphosorb® 950 mg) during their marketing on the German market.

Risk Management Plan
The applicant is of the opinion that a formal risk management plan is not necessary. The RMS agrees, as this is a well-known product.

Product information

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. There were two test rounds with a written questionnaire that included sufficient questions about the critical sections. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In addition, the participants were asked to give their opinion on 17 statements regarding the leaflet.

The package leaflet was adapted before the first round of testing to optimize the leaflet. A first test was performed with 16 participants and the results from 12 participants were evaluated. This lead to the following results: not all information was located and easily understood, especially the information relating to interactions, breast-feeding, starting dose and frequency of possible side effects. To improve the locatability and comprehensibility the format of the package leaflet and the layout (format and bold print) were changed after the first round.

The second test with the adapted text performed with 12 participants (the results of 11 participants were evaluated) led to the following major results: more than 90% of the participants was able to locate the information and more than 80% was able to give the correct answer. Also the time to finish the questionnaire was reduced.

Thus, after the first round, the patient information leaflet has been adapted sufficiently taking into account the results of the test, which is confirmed by the results of the second round. The conclusions are clear, concise and clearly presented.

Package leaflet

The package leaflet has been adapted taking into account the results of the user testing.

Labelling

The label of the immediate package is combined with the patient information leaflet. In the readability test it was remarked that it would be useful to draw the attention to this fact on the label of the immediate package so the patient knows where to find the leaflet. The RMS finds this suggestion useful and the MAH is requested to include such a reference.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Phosphosorb 660 mg has a proven chemical-pharmaceutical quality. The clinical efficacy of Phosphosorb 660 mg for the indication stated in the SPC may be concluded beyond any reasonable doubt. The safety aspects are well known and adverse events essentially concern the overdose of calcium, which can be well controlled by monitoring of its clinical use.

The MEB, on the basis of the data submitted, considered that Phosphosorb 660 mg, film-coated tablets demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. This bibliographical application of Phosphosorb 660 mg is considered acceptable.

The SPC is satisfactory from the clinical, preclinical and chemical-pharmaceutical point of view. The SPC, package leaflet and labelling are in the agreed templates.

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

The Board followed the advice of the assessors. Phosphosorb 660 mg, film-coated tablets was authorised in the Netherlands on 11 July 2006.

During the MRP some member states discussed the wording of the indication. Therefore, the indication was changed from the initial wording ‘Hyperphosphataemia in patients with renal insufficiency’ to ‘Hyperphosphataemia in patients with chronic renal insufficiency undergoing dialysis’.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 3 May 2007. The concerned member states mutually recognised the Dutch evaluation for the marketing authorisation.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 11 July 2006 to 10 July 2009.

The date for the first renewal will be: 11 July 2011.

The following post-approval commitments were made during the procedure:

Quality – Drug Product

- The MAH committed to submit certification for the active substance of compliance of the primary packaging with the new Note for Guidance on Plastic Primary Packaging materials, CPMP / QWP / 4359 / 03 after it becomes official.
- The MAH committed to store at least one batch per year for stability reasons under ICH conditions, valid at the moment of production.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
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
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
PTH	Parathyroid hormone
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