CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sorbisterit powder for oral/rectal suspension 90% m/m Fresenius Medical Care Deutschland GmbH, Germany

calcium polystyrene sulphonate

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/901/01/MR
Registration number in the Netherlands: RVG 10261

22 December 2009

Pharmacotherapeutic group:	drugs for treatment of hyperkalaemia and hyperphosphataemia
ATC code:	V03AE01
Route of administration:	oral / rectal
Therapeutic indication:	hyperkalaemia, in patients with acute and chronic renal insufficiency, including patients undergoing dialysis treatment.
Prescription status:	prescription only
Date of first authorisation in NL:	12 February 1985
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 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 member states have granted a marketing authorisation for Sorbisterit powder for oral/rectal suspension 90% m/m, from Fresenius Medical Care Deutschland GmbH. The date of authorisation was on 12 February 1985 in the Netherlands. The product is indicated for the treatment of hyperkalaemia in patients with acute and chronic renal insufficiency, including patients undergoing dialysis treatment.

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

Sorbisterit is a cation exchange resin which releases calcium in the intestines and binds potassium. This reduces the absorption and metabolic availability of potassium.
The calcium bound in the resin is exchanged for the potassium present in the intestines. According to various publications, 1 g of the exchange resin can bind 0.7 mmol potassium *in vivo*.

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 polystyrene sulphonate. 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 scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted.

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 substance
The active substance calcium polystyrene sulphonate is an established active substance described in the BP*. The drug substance is a cream to light brown fine powder, which is practically insoluble in water and ethanol. The drug substance is a cation-exchange resin prepared in the calcium form containing not less than 6.5% w/w and not more than 9.5% w/w of calcium.

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
Starting material is a sulphonated cross-linked polystyrene copolymer that is produced in bead form. The starting material is a readily available substance of commerce. The beads are purified followed by washing. By stirring with calcium chloride the resin is regenerated to the calcium form. After washing with water, the wet resin is dried, grinded and packaged. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Specification
The drug substance specification is in line with the BP, with additional requirements for particle size, odor and foreign matter. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability
Stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60% RH (48 months), 2 batches with unknown batch size, stored at 25°C/60% RH (12 months) and 3 batches with unknown batch size, stored at 40°C/75% RH (12 months). The batches were stored in the commercial packaging. As stability has been shown for 12 months accelerated conditions a retest period of 60 months, when stored not above 25°C in the proposed packaging material has been granted.
The MAH has committed to submit the long-term data up to 60 months.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
The product is a powder for oral suspension or for rectal suspension. According to the SPC up to 60 g of powder daily may be used. This corresponds to 108 mmol calcium per day (2 grams of calcium per day). One gram of powder contains 759 – 949 mg calcium polystyrene sulphonate, corresponding to 1.8 mmol calcium. The excipients are sucrose and anhydrous citric acid.
The product is packaged in LDPE/HDPE cans with a cap consisting of LDPE/HDPE material. A supplied spoon consists of transparent polystyrole. The packaging is usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients comply with Ph.Eur. requirements. The specifications for the excipients are acceptable.

Manufacturing process
The powder is prepared by a mixing process and has been adequately validated according to relevant European guidelines. Sufficient details on the manufacture are present. Process validation data on the product have been presented for 3 full scaled batches.

Product specification
The product specification includes tests appearance, filling weight, loss on drying, pH, potassium exchange capacity, bulk density, identity, assay of calcium and microbiological purity. The release and shelf-life requirements are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product

Stability data on the product has been provided for 3 full scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in the commercial packaging. The conditions used in the stability studies are according to the ICH stability guideline. No trend has been observed for any of the parameters at both conditions. A 3 year shelf-life, without special storage temperature, is acceptable in view of the available stability data. In-use data justify the in-use stability of 25 days after first opening.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Pharmacodynamics

Calcium resins exchange their calcium ions mostly for potassium ions. Although the affinity of the resins to calcium is higher than to potassium, the high concentration of potassium ions in the intestine induces the resin to release its calcium ions and to bind the potassium ions. Calcium has several functions in the human organism, structural and regulatory. In most patients serum calcium levels do not increase significantly after the administration of calcium resins. However, in rare cases hypercalcaemia may develop. It is therefore advisable to regularly control serum calcium levels. This point is adequately addressed in the SPC.

Pharmacokinetics

The polystyrene content of the resin is not absorbed in significant amounts and thus only distributes within the intestine. Cation exchange resins are excreted in faeces from 24 h to about 7 d after ingestion.
Calcium ions released from the resin are partly absorbed, although calcium absorption is impaired in patients with renal insufficiency. Calcium is a normal component of the human body, 99% is found in the bones in a crystalline state. This pool of insoluble calcium exchanges rapidly with cytosolic and extracellular calcium. The remaining 1% is distributed to the compartments of the extra- and intracellular space. Under physiologic conditions calcium is excreted in approximately equal amounts in urine and endogenous intestinal secretion. The calcium homeostasis is closely regulated. The main elimination route for surplus calcium is the renal excretion.

Toxicology

Toxicological data about calcium polystyrene sulphonate is limited. Calcium polystyrene sulphonate is considered as relatively non-toxic. The toxic effects of calcium salts are mild and essentially concern the overdose of calcium. The risk of the supplied calcium depends on the absorbed share and its bioavailability.
No *in vitro* or *in vivo* genotoxicity studies of calcium polystyrene sulphonate have been identified. No studies describing carcinogenic effects of Sorbisterit® or other calcium resins were found by searches in relevant databases. There were no reports found on the reproduction toxicity of calcium polystyrene sulphonate resins. High doses of dietary calcium were associated with reproduction toxicity in a variety of animal species (rats and mice).

Environmental risk assessment

The MAH has committed to provide an environmental fate and effect analysis for the medicinal product Resical after the granting of the marketing authorization, or otherwise to provide a motivation why such an environmental fate and effect analysis is not necessary.

II.3 Clinical aspects

Pharmacokinetics
Polystyrene resins are insoluble and non-absorbable. They are excreted in faeces from 24 hours to about 7 days after ingestion. Calcium released from the resin is partly absorbed. The electrolyte undergoes physiological pathways of absorption, distribution and elimination. Calcium polystyrene can reduce absorption of tetracycline and l-thyroxin. These interactions are all mentioned under section 4.5 of the SPC.

Pharmacodynamics
Cation resins exchange one cation for another. Calcium resins can exchange over 70% of their exchange capacity against potassium. It is estimated that 1 g of calcium polysterene sulphonate could bind 1.3 to 2 mmol of potassium, but it is not known whether this is really achieved in clinical practice.

Clinical efficacy
Data on efficacy obtained so far are adequately summarised in the clinical expert report. This application is based on well-established use. During years of experience and in several clinical investigations, Sorbisterit and other comparable calcium resins have shown to be very effective in maintaining serum potassium levels in normal ranges.

Clinical safety
The safety aspects of calcium polystyrene are well-known. Calcium overloading and hypercalcemia/hypokalemia may occur, although not often as patients with renal insufficiency generally higher risk for developing hypocalcemia. It may bind other cations such as magnesium and deficiencies may occur. Patients should be monitored for electrolyte disturbances, especially hypokalemia and hypercalcemia. Postmarketing data revealed no evidence of change in characteristics of listed ADR or unlisted reactions.

Risk management plan
In view of the existing knowledge and experience with the active substance calcium polystyrene sulfonate, the available data and the known risk benefit profile it is accepted that the MAH will perform the standard pharmacovigilance activities as described in volume 9 of 'The rules governing medicinal products in the European Union'.
An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment. If, in future, new data suggest differently the submission of a Risk Management Plan and a Risk Minimisation Plan can be necessary.

Benefit/risk assessment
Based on the data submitted, adequate evidence of efficacy has been demonstrated for the indication 'hyperkalaemia, in patients with acute and chronic renal insufficiency, including patients undergoing dialysis treatment' as well as a satisfactory risk/benefit profile.

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. The tested package leaflet was a literally English translation of the PIL in the RMS.

The first and the second readability tests were both written readability tests. This is considered acceptable. The first test was performed with 11 participants. This first test led to a revision in almost every section of the original text in which e.g.
- foreign words were avoided
- text brackets were avoided
- information sequences were changed
- information repetition was reduced.

The patient information leaflet has been adapted sufficiently taking into account the results of the first test.

The second test with the adapted text performed with 13 participants did not lead to a revision of the text. Participants located more than 90% of the questioned information and comprehensibility of the final version of the package leaflet was improved. The readability test concludes that the package leaflet is laid out clearly, and is easy to comprehend which allowed the participants to locate, comprehend and act appropriately on the information in the package leaflet.
It can be concluded that the readability of the patient information leaflet is of an acceptable level. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections and the conclusions were clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB, on the basis of the data submitted, considered that Sorbisterit powder for oral/rectal suspension 90% m/m provided adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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. Sorbisterit was authorised in the Netherlands on 12 February 1985.

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 20 March 2007. The concerned member states mutually recognised the Dutch evaluation for the marketing authorisation.

The SPC, package leaflet and labelling are in the agreed templates.

The PSUR submission cycle was started as a one-year interval on 20 March 2007, and will be extended to a 3-year interval in case of no major safety concerns after one year. The first PSUR will cover the period from March 2007 to March 2008.

The date for the first renewal will be: 20 March 2012.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH has committed to submit the end results (60 months) of the stability study on the three commercial scale batches in due time.

Environmental risk assessment

- The MAH has committed to provide an environmental fate and effect analysis for the medicinal product Resical after the granting of the marketing authorization, or otherwise to provide a motivation why such an environmental fate and effect analysis is not necessary.

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
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 name of the medinical product in Lithuania.	NL/H/0901/ 001/IB/001	IB	23-1-2008	22-2-2008	Approval	N
Change in the name of the medinical product in France.	NL/H/0901/ 001/IB/002	IB	23-1-2008	3-4-2008	Approval	N
Change in the name of the medinical product in Germany.	NL/H/0901/ 001/IB/003	IB	23-1-2008	22-2-2008	Approval	N
Change to comply with update Ph.Eur. regarding the excipient citric acid.	NL/H/0901/ 001/IA/004	IA	24-1-2008	7-2-2008	Approval	N