CBG MEB

Public Assessment Report

Scientific discussion

Biphozyl, solution for haemodialysis/ haemofiltration

(magnesium chloride hexahydrate, sodium chloride, potassium chloride, disodium phosphate dihydrate, sodium hydrogen carbonate)

NL/H/3002/001/DC

Date: 13 April 2015

This module reflects the scientific discussion for the approval of Biphozyl, solution for haemodialysis/haemofiltration. The procedure was finalised on 20 October 2014. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

ARF	Acute Renal Failure
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CRRT	continuous renal replacement therapy
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Biphozyl, solution for haemodialysis/haemofiltration from Gambro Lundia AB.

The product is indicated as replacement solution and as dialysis solution for treatment of acute kidney injury during continuous renal replacement therapy (CRRT). Biphozyl is used in a post-acute phase after initiation of renal replacement therapy when pH, potassium and phosphate concentration have returned to normal. Biphozyl is also used when other buffer sources are available as well as during regional citrate anticoagulation. Moreover, Biphozyl is used in patients with hypercalcaemia.

Biphozyl may also be used in cases of drug poisoning or intoxications when the substances are dialysable or filterable.

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

This decentralised procedure concerns a bibliographic application based on the well-established use of this replacement/dialysate solution. All of the drug substances have a well established use of more than 10 years in the EEA. Numerous haemodialysis/haemofiltration solutions exist and are widely used.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

II. QUALITY ASPECTS

II.1 Introduction

Biphozyl is a clear and colourless solution for haemodialysis/haemofiltration.

Theoretical osmolarity is 290 mOsm/l and pH = 7.0 – 8.0.

Biphozyl is presented in a two-compartment bag. The final reconstituted solution is obtained after opening the peel seal and mixing the contents of the two compartments.

The composition of the reconstituted solution is as follows:

Active substances		
Sodium, Na^+	140 mmol/l	140 mEq/l
Potassium, K^+	4 mmol/l	4 mEq/l
Magnesium, Mg^{2+}	0.75 mmol/l	1.5 mEq/l
Chloride, Cl^-	122 mmol/l	122 mEq/l
Hydrogen phosphate, HPO_4^{2-}	1 mmol/l	2 mEq/l
Hydrogen carbonate, HCO_3^-	22 mmol/l	22 mEq/l

The two-compartment bag is made of a multilayer film containing polyolefins and elastomers. The 5000 ml bag is comprised of a small compartment (250 ml) and a large compartment (4750 ml). The two compartments are separated by a peel seal. The bag is fitted with an injection connector (spike connector) made of polycarbonate (PC) and a luer connector (PC) with a frangible pin or a valve (made of silicone rubber) for the connection with a suitable solution line. The bag is overwrapped with a transparent overwrap made of polymer film. The solutions contained in the small compartment A (250 ml) and in the large compartment B (4750 ml) should be mixed immediately prior to use. The

small compartment contains only all magnesium chloride hexahydrate, the other constituenst are in the larger compartment.

The excipients are:

Small compartment -	Water for injections
	Dilute hydrochloric acid (for pH adjustment) E 507
Large compartment -	Water for injections
	Carbon dioxide (for pH adjustment) E 290

II.2 Drug Substances

The active substances are magnesium chloride·6 H2O, sodium chloride, sodium hydrogen carbonate, potassium chloride and disodium phosphate·2 H2O. They are all established active substances described in the European Pharmacopoeia (Ph.Eur.). The active substances are all soluble in water; they are all inorganic salts and are not expected to chemically change over time.

Full information has been provided for sodium hydrogen carbonate and disodium phosphate dihydrate.

For magnesium chloride hexahydrate, sodium chloride and potassium chloride the CEP procedure is used. 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

The description of the manufacturing processes of sodium hydrogen carbonate and disodium phosphate dihydrate, including flow diagrams, are presented in the dossier. For magnesium chloride hexahydrate, sodium chloride and potassium chloride reference is made to the CEP. Therefore no details on the manufacturing process have been included for these substances.

Quality control of drug substances

The drug substance specifications are in line with the Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data, demonstrating compliance with the Ph.Eur. specifications, have been provided.

Stability of drug substances

Stability data on the active substances have not been provided where CEPs are present and a re-test period is mentioned on the CEP. In cases that no re-test period is mentioned or no CEP is present, the supplier has provided data on the stability of the drug substance. A commitment is provided by the drug product manufacturer that all batches are re-tested periodically. Appropriate frequencies have been laid down.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known. This product concerns an application submitted under Article 10a (well-established use) of Directive 2001/83/EC. Therefore bioequivalence studies were not conducted.
The main development studies performed are stability studies to investigate the behaviour of the solution in the proposed polyolefin packaging (bags and tubes). Safety of potential leaching products has been discussed. The pharmaceutical development of the product has been adequately performed.
Autoclaving has been chosen as sterilisation method in line with the European guideline “Decision trees for the selection of sterilisation methods”. This is appropriate. The product does not contain any added anti-microbiological preservatives. The sterility and bacterial endotoxin tests as per the

requirements of European Pharmacopoeia are carried out at release and shelf-life. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing consists of preparing of the bulk solution, sterile filtration, filling of the bag compartments one after another, printing and wrapping of the bag and autoclaving. Sufficient information has been provided with regard to (pre)filter details, closures and in-process control values.

The manufacturing process has been validated with production batches of a comparable product (Primasol, registered through FR/H/0226/001-002) and performed on two full-scale batches on both compartments of the bag and the reconstituted solution. This solution differs from the drug product Biphozyl in the absence of phosphate and the presence of glucose. This is considered to be of no consequence to the validation of the manufacturing process. Moreover, in-process control results have been provided of the two production-scale batches of the product at issue together with batch analysis results of two production-scale batches for each packaging. As marginally different products have been manufactured at the same site according the same standard manufacture process for years, the provided information is sufficient for validation of the manufacture process.

The SD1 two-compartment polyolefin bags are filled during the manufacturing process using the inlet tubes respectively located at the top and at the bottom of each compartment. The small compartment A is closed with the stopper and the large compartment B with the spike connector and a luer connector.
The solution in the small compartment A will never be infused directly to the patient. It will always be mixed with the solution in the large compartment B before use.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes several identification tests, a test for appearance, pH, aluminium, particulate contamination, extractable volume, sterility, bacterial endotoxins and assay. The release and shelf-life limits for the reconstituted solution are identical except for extractable volume, for which a tighter limit is set at release, to certify compliance with the shelf-life specification during the whole shelf life. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three industrial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three full-scale batches of a very similar product (Phoxilium, registered through DCP NL/H/1147/001) that has been stored at 30°/65% RH (18 months) and 40°C/40% RH (9 months). These batches were stored in the proposed polyolefin packagings. The conditions used in the stability studies are not according to the ICH stability guideline for a product packed in a semi-permeable container. However, in line with that same guideline weight loss at 25°C/25%RH and 30°C/40%RH has been calculated. The results justify the accepted shelf life of 18 months.
Moreover, stability data on Biphozyl have been provided, for 3 batches. The results show that after storage for 6 months at 40°C±2°C/40%±5% RH and after 6 months at 30°C±2°C/65%±5% RH all the tested parameters are stable and within the limits for the tested polyolefin material.
The granted shelf life, packaging material and storage conditions are: 18 months; in polyolefin bags; Do not freeze.
It has been demonstrated that the product remains stable for 24 hours following reconstitution, when stored at room temperature.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Biphozyl, solution for haemodialysis/haemofiltration has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to place three batches of Biphozyl on stability study (at 4°C, 30°C and 40°C); these will be followed for 24 months.
- The MAH committed that one batch per year of haemofiltration solutions containing phosphate and packaged in two compartment polyolefin bags will be put on stability (30 ± 2ºC/65 ± 5% RH) during the shelf-life of the product (18 months) in order to secure that there are no deviations in production.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

From a pharmacodynamic point of view, the drug product Biphozyl after reconstitution is not pharmacologically active. The drug substances contained in replacement solutions for haemofiltration and haemodiafiltration are normal constituents of the physiological plasma and their concentrations in the solutions are only aimed to restore or normalize the plasma acid-base and electrolyte balance. Therefore, no adverse effects are expected by their correct use.
Bicarbonate, the physiological buffer of the body, is used as an alkalizing buffer.
Bicarbonate is preferred in patients with lactic acidosis. Continuous Renal Replacement Therapy (CRRT) is a short-term treatment and it is considered as a life-saving technique. In addition, there is a consensus that patients with severe Acute Renal Failure (ARF) should be treated with continuous renal replacement therapy.
The drug substances in Biphozyl after reconstitution, are normal constituents of the human plasma, and are described in current Ph. Eur. Monograph 0861 “Solutions for haemofiltration and haemodiafiltration´, except for hydrogen phosphate content which though is present in a concentration similar to that one in human plasma.. Therefore, additional pharmacodynamic studies are not applicable or necessary in this context.

III.2 Pharmacokinetics

The drug substances are physiological electrolytes, and their concentrations are usually adjusted in the solution in order to normalize those in the serum of ARF patients. The treatment and the choice of the appropriate solution are adapted to each patient according to his/her clinical status. Therefore, pharmacokinetic studies are not applicable or necessary in this context and should not be required.

III.1 Toxicology

The drug substances are normal constituents of animal and human blood and have been used in the chronic treatment of renal failure as dialysis fluids for decades. The drug substances in Biphozyl after reconstitution, are described in current Ph. Eur. monograph 0861 “Solutions for haemofiltration and haemodiafiltration”, except for the hydrogen phosphate content which is present in a concentration similar to that one in human plasma. Dialysis solutions have been used for many years worldwide, e.g. the already approved products. Therefore toxic effects are not expected at physiological doses by their therapeutic use. Justifications for the use of the drug substances are reported. No toxic effects are expected at therapeutic doses. Therefore, preclinical safety data are considered not relevant in this scenario.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Electrolytes are unlikely to result in a significant risk to the environment. According to the guideline on the environmental risk assessment of medicinal products for human use, an environmental risk assessment is not needed for this product (EMEA/CHMP/SWP/4447/00).

III.3 Discussion on the non-clinical aspects

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 for this well-established medicinal product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Magnesium chloride hexahydrate, sodium chloride, sodium hydrogen carbonate, potassium chloride, disodium phosphate dihydrate are well-known active substances with established efficacy and tolerability.

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 member states agreed that no further clinical studies are required.

Pharmacokinetic studies are not relevant, as constituents of these solutions are naturally and physiologically occurring electrolytes and water.

IV.2 Clinical efficacy

Sufficient support can be found in the literature for the specific composition and concentrations of electrolytes in the Biphozyl solution if it is used in the post-acute phase of the treatment with different continuous renal replacement therapy (CRRT) techniques in acute renal failure. The solution is designed more specifically (and is suitable) for use in combination with regional anticoagulation of the extracorporeal circuit offering a relative low concentration of hydrogen carbonate and also by absence of calcium. Because of the absence of calcium this medicine should also be quite suitable for use with CRRT in the treatment of patients with hypercalcaemia.

There is no indication from the literature that the efficacy in elderly patients or in children should be different from the efficacy in adults and adolescents. Neither is there an indication of influence of race. Overall the information obtained from the bibliographic search in the published literature offers sufficient support for the efficacy that has to be expected from the use of Biphozyl solution specifically in the post-acute phase of CRRT, in combination with regional citrate anticoagulation. It is not suitable for the acute phase of CRRT.

IV.3 Clinical safety

From the relevant literature it comes forward that CRRT treatment based on hemofiltration using replacement/dialysate solutions comparable to Biphozyl, can be safely managed under the guidance of experienced physicians and nursing staff. There is no indication so far that the outcome of the procedures is associated with the age of the patients. Because of the specific composition of Biphozyl it is important to state that this solution should only be indicated in the post-acute phase of the treatment to avoid safety problems with hyperkalaemia and hyperphosphataemia.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Biphozyl.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypervolaemia

	Hypovolaemia Acid-base imbalances (acidosis, alkalosis) Electrolyte imbalances (incl. hypocalcaemia, hyperkalaemia, hyperphosphataemia)
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the well-established use of Biphozyl, solution for haemodialysis/haemofiltration. This has been adequately demonstrated based on literature data. No new clinical studies were conducted. Risk management is adequately addressed. The member states consider the benefit-risk balance of this replacement/dialysate solution positive in the proposed indication.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. Instead a bridging has been performed between the daughter package leaflet for Biphozyl and the parent PL for the products Phoxilium (content) and Prismocitrate (design and layout). Both parent package leaflets have been successfully tested with user consultation. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Biphozyl, solution for haemodialysis/haemofiltration has a proven chemical-pharmaceutical quality and its use is considered well-established in the approved indications:

‘as replacement solution and as dialysis solution for treatment of acute kidney injury during continuous renal replacement therapy (CRRT). Biphozyl is used in a post-acute phase after initiation of renal replacement therapy when pH, potassium and phosphate concentration have returned to normal. Biphozyl is also used when other buffer sources are available as well as during regional citrate anticoagulation. Moreover, Biphozyl is used in patients with hypercalcaemia.
Biphozyl may also be used in cases of drug poisoning or intoxications when the substances are dialysable or filterable.’

Adequate non-clinical and clinical overviews have been provided.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the use of Biphozyl is well-established, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 2014.

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