

## PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

### Phoxilium 1.2 mmol/l phosphate solution for haemodialysis/haemofiltration GAMBRO Lundia AB, Sweden



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/1147/001/DC**  
**Registration number in the Netherlands: RVG 101928**

**25 January 2010**

Pharmacotherapeutic group:	hemofiltrates
ATC code:	B05ZB
Route of administration:	intravenous; haemodialysis
Therapeutic indication:	CRRT in critically ill patients with ARF when pH and kalemia have been restored to normal and when the patients need phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT; drug poisoning or intoxication.
Prescription status:	prescription only
Date of authorisation in NL:	19 August 2009
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, 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 Phoxilium 1.2 mmol/l phosphate solution for haemodialysis/haemofiltration, from GAMBRO Lundia AB. The date of authorisation was on 19 August 2009 in the Netherlands.

The product is indicated for CRRT (continuous renal replacement therapy) in critically ill patients with ARF (acute renal failure) when pH and kalaemia have been restored to normal and when the patients need phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT.

Phoxilium may also be used in cases of drug poisoning or intoxications when the poisons are dialysable or pass through the membrane.

Phoxilium is indicated for use in patients with normal kalaemia and normal or hypophosphataemia.

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

Phoxilium, solution for haemofiltration and haemodialysis, is pharmacologically inactive. The sodium, calcium, magnesium, potassium, phosphate and chloride ions are present at concentrations similar to physiological concentrations in normal plasma.

Phoxilium is used to replace water and electrolytes removed during haemofiltration and haemodiafiltration or to serve as a suitable dialysis solution for use during continuous haemodiafiltration or continuous haemodialysis. Hydrogen carbonate is used as an alkalinising buffer.

Acute renal failure is a common complication of critical illnesses with mortality in excess of 50%. Therapy for intrinsic ARF is primarily supportive, with no effective pharmacologic therapy for renal failure due to acute tubular necrosis. Various procedures for renal replacement therapies have been studied during the last fifty years.

Continuous renal replacement therapy has taken the major part in this setting, either as haemofiltration, haemodialysis or haemodiafiltration. Different solutions are used, taking into account patient condition and physician's preferred procedure, either to compensate for water and electrolytes losses through ultrafiltration (convection) or to be used as a dialysate to set an appropriate concentration gradient (diffusion) across the dialysis membrane.

Three main procedures are used for CRRT, whose definitions according to the Acute Dialysis Quality Initiative are listed as follows:

- Haemofiltration (HF): an extra-corporeal, primarily convective therapy, where solute and water are transferred across a semi-permeable membrane. Replacement fluid is used to achieve fluid balance.
- Haemodialysis (HD): an extra-corporeal, primarily diffusive therapy, where solute and water are transported across a semi-permeable membrane into dialysate.
- Haemodiafiltration (HDF): a technique associated with high ultrafiltration rates and diffusion across a highly permeable membrane. Blood and dialysate are circulated as in haemodialysis, but in addition, ultrafiltration, in excess of the scheduled weight loss, is provided. Replacement fluid is used to achieve fluid balance.

The marketing authorisation is granted based on article 10a (well-established medicinal use) of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of phosphate supplementation during CRRT. 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 MAH consulted the Medical Products Agency (MPA) of Sweden for scientific advice in Uppsala on 24 October 2006. The MPA had no difficulty on the concept of a bibliographical application classification to be registered by a decentralized procedure, provided that literature references support phosphate supplementation and that well established use (more than 10 years) is documented either in renal failure or any other condition. Proposed indications were also discussed. Following this scientific advice, additional literature references were searched for on phosphate supplementation in conditions other than renal failure.

Regulatory advice was sought from MEB as the Netherlands was selected as the reference member state. A bibliographical application was considered adequate provided references support the claim.

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 substances**

The active substances are Calcium chloride-2 H<sub>2</sub>O, Magnesium chloride-6 H<sub>2</sub>O, Sodium chloride, Sodium hydrogen carbonate, Potassium chloride and Disodium phosphate, 2 H<sub>2</sub>O. These are all established active substances described in the European Pharmacopoeia (Ph.Eur.\*). The active substances are all soluble in water. The active substances are all inorganic salts and are not expected to chemically change over time.

#### Manufacture

A description of the manufacturing processes including flow diagrams has been provided for all substances.

#### Specification

The drug substance specifications are in line with the Ph.Eur. For sodium chloride an additional requirement for bacterial endotoxins has been included. The specifications are 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 for all substances.

#### Stability

Stability data on the active substances have not been provided, since the active substances are simple inorganic salts and are not expected to chemically change over time. This is acceptable in view of the Active Pharmaceutical Ingredients Committee "How to do" Document – Interpretation of the ICH Q7a Guide, version 5, November 2006, section 1.5.1. A commitment is made that all batches are re-tested each year.

\* *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

Phoxilium is a solution for haemofiltration, packed in a two-compartment bag (5000 ml) with a small and a large compartment. The solutions in the small compartment A (250 ml) and the large compartment B (4750 ml) should be mixed immediately prior to use. The two compartments are separated by a frangible pin or a peel seal.

The quantitative composition before reconstitution is listed below.

1000 ml of solution in the small compartment (A) contains:

Calcium chloride, 2 H <sub>2</sub> O	3.68 g
Magnesium chloride, 6 H <sub>2</sub> O	2.44 g

1000 ml of solution in the large compartment (B) contains:

Sodium chloride	6.44 g
Sodium hydrogen carbonate	2.92 g
Potassium chloride	0.314 g
Disodium phosphate, 2 H <sub>2</sub> O	0.225 g

The quantitative composition after reconstitution is listed in the table below.

<b>Quantitative composition of the reconstituted solution</b>			
		<b>in mmol/l</b>	<b>in mEq/l</b>
Calcium	Ca <sup>2+</sup>	1.25 mmol/l	2.50 mEq/l
Magnesium	Mg <sup>2+</sup>	0.600 mmol/l	1.20 mEq/l
Sodium	Na <sup>+</sup>	140.0 mmol/l	140.0 mEq/l
Chloride	Cl <sup>-</sup>	115.9 mmol/l	115.9 mEq/l
Phosphate	HPO <sub>4</sub> <sup>2--</sup>	1.20 mmol/l	2.40 mEq/l
Hydrogen carbonate	HCO <sub>3</sub> <sup>-</sup>	30.0 mmol/l	30.0 mEq/l
Potassium	K <sup>+</sup>	4.00 mmol/l	4.00 mEq/l

The solution has a theoretical osmolality of 293 mOsmol/l and a pH of 7.0-8.5.

The excipients are:

*Small compartment A*

Water for injections

Hydrochloric acid (for pH adjustment)

*Large compartment B*

Water for injections

Carbon dioxide (for pH adjustment)

The container made in poly(vinyl chloride) (PVC) or polyolefin is a two-compartment bag. The large compartment B is fitted with a spike connector made of polycarbonate, which is closed with a rubber disc covered by a cap as well as a polycarbonate luer connector with a frangible pin for the connection of the bag with a suitable replacement solution line or dialysate line.

The bag is overwrapped with a transparent overpouch made of a multilayer polymer film.

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients comply with their Ph.Eur. monographs. The main development studies performed investigate the compliance of the solution with the three proposed polyolefin packagings (bags and tubes) and the PVC packaging (bag and tubes). Safety of potential leaching products has been certified.

The pharmaceutical development of the product has been adequately performed.

#### Manufacturing process

The manufacturing process consists in preparing the bulk solution, filling of the bag with sterile filtration, wrapping of the bag and autoclavation.

The manufacturing process has been validated with production batches of a comparable product and performed on two full scaled batches on both compartments of the bag and the reconstituted solution. This solution differs from the drug product 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 to the same standard manufacture process for years, the provided information is considered sufficient for validation of the manufacturing process.

#### Quality control of drug product

The product specification includes tests for fill in appearance, identity, 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 a tightened release specification of extractable volume in order to comply 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 two full-scale batches in polyolefin bags and two full-scale batches in PVC bags, demonstrating compliance with the release specification.

Stability tests on the finished product

Stability data on the product have been provided for three full-scale batches stored at 30°/65% RH (18 months) and 40°/40% RH (9 months). These batches were stored in all proposed polyolefin packagings and the PVC packaging. 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 this guideline weight loss at 25°C/25%RH and 30°C/40%RH has been calculated. The results justify a shelf life of 18 months at 4-30°C, with the storage condition 'do not refrigerate or freeze'.

In-use stability data has been provided demonstrating 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.2 Non clinical aspects**

Phoxilium, 1.2 mmol/l phosphate solution for haemodialysis/haemofiltration does not contain any new drug substances. Therefore, a bibliographical application based on literature is appropriate and no non-clinical studies were submitted. The provided non-clinical overview is adequate. The safety and effectiveness of dialysis/replacement solutions containing physiological levels of sodium, magnesium, potassium, calcium, chlorides and bicarbonate, are based mainly on extensive clinical experience.

**Environmental risk assessment**

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

**II.3 Clinical aspects**

**Pharmacology**

The major aims of CRRT in ARF are detoxification, correction of acidosis, water removal and restoration of physiologic concentrations of electrolytes. The choice of fluids for CRRT is a determinant in the achievement of these goals, but the operational conditions of CRRT also have an impact. Fluids used for CRRT are sterile solutions that generally contain electrolytes in concentrations similar to their unbound concentrations in blood plasma, and may or may not contain glucose.

These CRRT solutions do not contain any pharmacologically active drug substances or ingredients. These solutions are only used to restore normal plasma concentrations of electrolytes, euolemia, and acid-base balance.

In fact, in a complex situation like ARF, in which co-morbid conditions strongly influence prognosis, supportive CRRT is only a part of the treatment for the patient. The efficacy of CRRT is often assessed on surrogate end-points (e.g., solute concentrations or clearances, volume removal) since definitive end-points such as cure or survival rely on many factors. Most efficacy studies on definitive clinical end-points also report results regarding electrolyte concentrations.

There is no clear distinction in the published literature between pharmacologic studies and efficacy studies when testing these solutions. Therefore, all types of studies are included in the "Clinical Efficacy" section of this report for the sake of convenience and completeness.

Pharmacokinetic studies as well, are not relevant for the proposed Phoxilium solution since its electrolyte components are within normally occurring physiological concentrations.

**Clinical efficacy**

With respect to the composition of the Phoxilium solution, electrolyte concentrations have been selected on the basis of the needs for a kind of "post-acute" phase of CRRT therapy when pH and kalaemia have been restored to normal and when the patient needs phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT.

The three formulations already on the market in Europe are described in Table 1 together with the new Phoxilium formulation. In Table 1 these solution formulations are compared to normal plasma concentrations.

**Table 1: Electrolyte Concentrations of Replacement / Dialysate Solutions**

	HCO <sub>3</sub> <sup>-</sup> mmol/l	Lactate mmol/l	Ca <sup>2+</sup> mmol/l	Mg <sup>2+</sup> mmol/l	K <sup>+</sup> mmol/l	Na <sup>+</sup> mmol/l	Cl <sup>-</sup> mmol/l	PO <sub>4</sub> <sup>2-</sup> mmol/l	Glucose mmol/l
Hemosol B0	32	3	1.75	0.5		140	109.5		
Primasol 2 mmol/l potassium	32	3	1.75	0.5	2	140	111.5		6.1
Primasol 4 mmol/l potassium	32	3	1.75	0.5	4	140	113.5		6.1
Phoxilium	30		1.25	0.6	4	140	115.9	1.2	

The addition of Phoxilium will increase the variety of CRRT solutions. It will be used during CRRT in which the patient's clinical conditions are closely monitored under the supervision of nephrologists. The major clinical concerns during CRRT deal with mass balance of electrolytes and fluid during the treatment and to maintain these electrolyte concentrations at physiological concentrations. Since these concerns are reported on extensively in the literature with respect to homeostasis of phosphate during CRRT, no clinical trial is needed for Phoxilium.

Since the formulation of Phoxilium solution is based on concentrations of electrolytes already in commercial use, this application is supported by a review of published literature and refers to the other formulations registered in the Hemosol / Primasol line. There was no specific clinical trial initiated by the MAH for the development of the Phoxilium formulation. CRRT replacement solutions for haemofiltration and haemodiafiltration with formulations similar to those of Hemosol B0 / Primasol replacement solutions have been in use worldwide for many years. There is extensive clinical experience provided in the scientific literature which has demonstrated these solutions to be both safe and effective when used as replacement solutions for CRRT.

Well established use of phosphate supplementation has been documented for more than 10 years in patients with renal failure requiring renal replacement therapy as well as in patients without severe renal failure, but in acute conditions where severe hypophosphatemia may occur or when enteral or parenteral nutrition is prescribed.

The clinical documentation retrieved from the literature is based on 29 published studies that involve 1291 patients with acute renal failure. In table 2, the following is listed: treatment type, reason for treatment and number of children included in these published studies on renal replacement therapy.

**Table 2: Number of Patients Per Treatment and Disease**

Treatment/ disease		ARF	ARF children	ESRD	Poisoning	Total
Therapy	Procedure					
HF	CRRT	725	59		2	786
	IT			24		24
HDF	CRRT	223			1	224
	IT			29		29
HD	CRRT	58			3	61



	IT	6		161		167
Total		1012	59	214	6	1291

**Table 3: Number of Patients in Studies on IV Phosphate Supplementation, RRT excluded**

Condition	Age	Number of studies	Number of patients	Number of patients with phosphate supplementation
Hypophosphatemia related to various conditions	Children	1	35	13
	Adults	8	195	168
Nutrition support	Adults	5	191	180
	Total	14	421	361

Fourteen studies not performed in renal replacement therapy (RRT) but reporting on phosphate supplementation, have been taken into consideration as well, and are summarized in table 3. These report on 421 patients, 361 of which were treated with IV phosphate supplementation.

Justification for the use of bicarbonate as a buffer

Bicarbonate is the buffer which has been used and approved for Hemosol B0 and PrismaSol 2 mmol/l or 4 mmol/l Potassium. Bicarbonate has been proven effective as a buffer for HF replacement solutions in a number of studies. Bicarbonate-buffered replacement solutions may be especially desirable and prescribed when liver function is compromised in patients with lactate intolerance or circulatory shock (Davenport et al, 1989). The bicarbonate concentration in the solution reported in these studies ranges from 30 mEq/l up to 40 mEq/l with or without 3 mEq/l of lactate. The proposed concentration of bicarbonate in Phoxilium (30 mmol/l) is within the low range of concentrations reported in the literature and is in the range specified by Ph. Eur. monograph 861 Solutions for haemofiltration and haemodiafiltration.

It should be also considered that with a tendency towards prescription of high volumes of ultrafiltration in the CRRT medical community, total daily base intake will also increase (Bellomo, 2002) and that a formulation with 4 mmol/l potassium and 1.2 mmol/l phosphate is intended for patients when acidosis has been corrected or is not a problem, which is usually the case in intoxications and in patients with normal renal function.

Justification for the Calcium Concentration

Calcium is provided in Phoxilium solution in a concentration (1.25 mmol/l) similar to normal free ionized Ca<sup>2+</sup> plasma concentration. To assess the role of the calcium concentration in the solution, most data come from HD studies and pharmacologic studies and address cardio-vascular endpoints and Parathyroid Hormone (PTH) regulation in end-stage renal disease (ESRD) that are not relevant to ARF.

In the published literature, calcium concentrations in replacement solutions for HF are usually in the range of 1.5 to 2 mmol/l and some report on calcium free solutions. However, since Phoxilium is considered a CRRT "maintenance" solution, it was deemed more appropriate to limit concentration in this solution to the physiological range of plasma free ionized calcium (1.06- 1.29 mmol/l).

Justification for the Magnesium Concentration

With respect to magnesium, dialysate and replacement solution concentration in Phoxilium (0.6 mmol/l) is similar to the normal free, diffusible concentrations of magnesium in plasma and formulated in accordance with what is reported in the literature.

Justification for the Potassium and Phosphate Concentrations

*With Respect to Potassium Concentrations:*

Commercial dialysate/replacement solutions used at the start of CRRT are usually potassium and phosphate free since most patients with ARF require potassium and phosphate removal at the time of CRRT initiation. Patients, especially those who receive CRRT for several consecutive days, will require potassium and/or phosphate supplementation, in addition to that administered in nutrition (Davenport, 2004).

Serum potassium and phosphate concentrations are typically increased at the time of CRRT initiation (Dolson, 1991). It is, thus, desirable to use potassium-free dialysates and replacement solutions followed by potassium-containing solutions when the plasma concentrations are normalized.



*With Respect to Phosphate Concentration:*

Available observational studies document the high frequency of abnormal phosphatemia values (mainly hyper) in continuous veno-venous haemodiafiltration (CVVHDF) as well as in continuous veno-venous haemofiltration (CVVH) (Morimatsu et al, 2002). The risk of hypophosphatemia must be considered. The precautions section of the labeling text of PrismaSol solutions, as recently approved by the FDA, states that "abnormalities in plasma phosphate concentration, especially hypophosphatemia, may also occur. Hypophosphatemia may require phosphate supplementation to maintain plasma concentrations in the physiological range". Hypophosphatemia is a well-known problem in acute or chronic renal failure in circumstances such as refeeding or tissue anabolism.

Frequency of hypophosphatemia in a retrospective study stands between 5.6% for IHD and 9.3% for CVVHDF (Tan et al, 2001). Need for phosphate supplementation in the replacement fluid reached 70% in a study on 20 consecutive patients with CVVH.

In another study on CVVH with 2 l/h ultrafiltration, phosphate loss was estimated at 1.7 mmol/h. This helps to estimate the need for phosphate supplementation in CRRT replacement and dialysis solutions.

Comparative clearances of phosphate with intermittent haemodialysis (IHD), sustained low-efficiency dialysis (SLED) and CVVH have been published (Ratanarat et al, 2005). The duration of treatment was the only factor determining phosphate removal. During CVVH, estimates of phosphate removal were  $66.7 \pm 18.9$  mmol/24h.

The feasibility of adding a mixture of mono and dibasic sodium phosphate has been reported in the early eighties (Ing et al, 1983) and Lentz, as early as in 1978, recommended adding 0.65 to 1.29 mmol/l of phosphate to haemodialysis bath to prevent hypophosphatemia.

When phosphatemia was lower than normal, Kohn (1995) reported two cases of lactic acidosis treated with CRRT when phosphate supplementation in the dialysate was initiated with 0.8 mmol.

Troyanov (2004) reported a clinical study on 20 consecutive patients treated with CRRT in a medico-surgical intensive care unit using phosphate addition to dialysate and replacement fluid when serum phosphate was less than 1.5 mmol/l. Of the 20 patients studied, 14 received more than 24 h of phosphate supplementation to dialysate and replacement solutions. Mean duration of supplementation was  $4.7 \pm 3.4$  days.

This group was composed of 10 males and 4 females with a mean age of  $62.5 \pm 10.4$  years. The most frequent etiology was acute tubular necrosis.

Hemodynamic instability was the main reason for choosing CRRT rather than IHD.

Dialysis fluid flow rate was 1000 ml/h and haemofiltration ultrafiltrate flow rate was 1000 ml/h in predilution.

Phosphate was added at the initiation of CRRT in 6 cases and after  $25.5 \pm 18.9$  h (range 7-58 h) in the other 8 patients. Serum phosphate level remained stable in all, but one patient who developed hyperphosphatemia after having inadvertently received an oral phosphate laxative (mean phosphate concentration  $1.27 \pm 0.10$  at day 0 and  $1.43 \pm 0.24$  at day 5).

No adverse event was noted on potassium, calcium, pH and bicarbonate homeostasis.

Phosphate supplementation with 1.2 mmol/l thus proved to be an effective and safe method to prevent hypophosphatemia in CRRT patients.

CRRT is on occasion used for the treatment of acute poisonings. Often times in poisoning cases, patients present themselves with normal renal function and normal plasma concentrations of phosphate. In these patients and in the absence of ARF-induced hyperphosphatemia, the use of a dialysate or replacement solution containing phosphate is desirable in order to prevent hypophosphatemia. This has been proposed by Chow (1997) in haemodialysis for ethylene glycol intoxication by adding 1.3 to 2.6 mmol phosphate in this dialysate. Dorval (1999), for the same reason added 9 mmol of phosphate IV per hour and recommended a phosphate-containing dialysate (1 mmol/l) during haemodialysis for methanol intoxication.

Occasionally patients with ESRD may present themselves with hypophosphatemia. Correction by haemodialysis has been reported by Kaye using calcium free dialysate supplemented with 1 or 2 mmol/l phosphate.

Severe refeeding hypophosphatemia has been reported in a patient with ESRD treated by continuous ambulatory peritoneal dialysis (CAPD). Intravenous phosphate (6 mmol) was administered but the patient died too early to assess the response to phosphate administration (Kurtin & Kouba, 1987).

Profound hypophosphatemia is not rare in the course of acute renal failure patients requiring dialysis when nutritional support is provided. Kurtin and Kouba reviewed 19 of such patients with various forms of nutritional support and found 4 cases with hypophosphatemia (serum phosphate =  $0.26 \pm 0.26$  mmol/l). Patients on total parenteral nutrition were given potassium phosphate and those tube fed were given a preparation with phosphate.

Besides CRRT, there is considerable experience with intravenous (IV) phosphate supplementation in hypophosphatemia of various origins or in nutritional support which has been proved effective and safe. Nine studies, mostly regarding intensive care unit (ICU) patients with hypophosphatemia, and supplementation with doses of 10 to 205 mmol of phosphate in 24h are reported.

Further, 5 nutritional support studies are listed regarding phosphate supplementation with up to 120 mmol/day for up to 22 days as refeeding hypophosphatemia is a well-known problem in patients starting nutritional support.

*Conclusion on phosphate supplementation:*

There is a wide experience to demonstrate that IV phosphate supplementation is effective in correcting hypophosphatemia in various conditions including ICU patients and nutritional support. With respect to the use of phosphate supplementation in CRRT (HF, HDF or HD) the need for phosphate supplementation will appear during the course of treatment since phosphate removal by HF, HDF or HD will require compensation, at least in some patients and especially in such conditions as intoxications where initial phosphatemia stands in the normal range.

Justification for the Sodium and Chloride Concentrations

The Phoxilium sodium concentration is within the normal range of plasma concentrations (135-146 mmol/l) and is the same as the ones used in PrismaSol and Hemosol formulations, which have been previously approved for sale. Chloride is only changed in the Phoxilium formulation based on the relative amount of the other electrolytes.

Justification for the Absence of Glucose in the Solution

Regarding the concentration of glucose in Phoxilium, most published studies used replacement solutions without glucose while a few used replacement solutions with 5.5 mmol/l of glucose. Hemosol B0 is a glucose-free solution and PrismaSol 2 and 4 mmol/l Potassium are solutions with 6.1 mmol/l of glucose.

As reported in the literature, when determining which concentration of glucose to use in the dialysate and/or replacement solution, one should consider the glucose loss in the ultrafiltrate (Bellomo et al, 1992; Heering et al, 1999), and that prevention of hyperglycemia is a prognostic factor in ICU patients.

It was thus deemed preferable by the MAH to provide a glucose free solution that would accommodate diabetic patients as well. Glucose supplementation can be provided, when needed, by other infusions or by nutrition.

Comparison of results in subpopulations

*Older people*

With respect to patient distribution by age, many of the articles surveyed only report mean age  $\pm$  standard deviation and do not report the distribution of age nor specify the results in patients over the age 65 or 75 years.

However, studies in critically-ill patients with ARF have a mean patient age around 60 years and should have at least part of the population over 65 and even 75 years.

*Children*

The literature survey in this dossier included three haemofiltration studies performed in pediatric patients. The ages of these patients ranged from newborn to 17 years of age. The studies were conducted to demonstrate that CRRT haemofiltration could be used to treat children with ARF. The Phoxilium formulation is somewhat different from the formulations used to treat these pediatric patients, but electrolyte homeostasis was maintained by IV supplementation. Even though fluid composition is not always reported, there is a wide experience of pediatric use of CRRT in multi-organ dysfunction syndrome either as CVVH, CVVHDF or CVVHD. IV phosphate supplementation has also been studied in children with ketosis, although efficacy of doses of 0.15-0.9 mmol/kg was questioned.

### *Intoxication*

Two studies report treatment of amanita mushroom or pentobarbital intoxication with HF or HDF. Another study with solutions in the PrismaSol concentration range except for glucose (as it was a peritoneal dialysis solution) reports positive results in lithium poisoning treated by CAVHDF or CVVHDF. Two other papers recommend using phosphate supplementation solutions for dialysis in ethylene glycol or methanol intoxication. In these intoxication situations, it would be appropriate to use a solution like Phoxilium whose electrolyte composition is in the normal plasma range.

### *Analysis of Clinical Information Relevant to Dosing Recommendations*

Treatment dose during CRRT is determined by the physician and is adjusted according to the patient's clinical status, blood chemistries (i.e. blood urea nitrogen, creatinine, potassium, etc.), and fluid removal needs. Replacement fluid volume/ultrafiltration-based dose is not always reported in haemofiltration studies. A variety of ultrafiltration rates have been reported, ranging from 1 l/h or less to 2 l/h or more than 2.5 l/h for a 70kg patient up to 4.5 l/h in experimental clearance assessment.

Over the years and with the acquisition of more experience by the medical community with CRRT, there has been a tendency to increase the dose delivered since it has been shown to positively correlate with survival. This observation was supported by the prospective randomized study by Ronco et al (2000). This study has the largest number of patients and addresses the relationship between delivered dose and outcome in ARF patients treated with CRRT. It is important to note that all patients in this study were treated with CVVH. It is also important to note that a study performed in a large ICU population indicated that many patients are prescribed an insufficient dose of CRRT and that the dose delivered may be considerably lower than what is prescribed.

Regarding HDF, dialysate flow rates have been reported in the 1 l/h range and replacement solution flow rates in the 750 ml/h to 2.5 l/h range when specified.

Regarding HD, dialysate flow rates less than 1 l/h have been reported in older studies. However, more contemporary studies generally report dialysate flow rates in excess of 1 l/h and up to 2.5 l/h.

### *Persistence of Efficacy and/or Tolerance Effects*

No articles could be found in the literature which addressed the persistence of efficacy and/or tolerance effects. In the study by Ronco et al (2000), more than 90% of surviving patients were reported to have restoration of renal function before discharge.

### MEB conclusion on efficacy

The Phoxilium formulation is in the range specified by Ph. Eur. monograph 861 *Solutions for haemofiltration and haemodiafiltration*. The composition of the Phoxilium solution and electrolyte concentrations have been selected on the basis of the needs for a kind of "post-acute" phase of CRRT therapy in critically ill patients with ARF when pH and kalaemia have been restored to normal and when the patient needs phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT.

Phoxilium will be used during CRRT in which patient's clinical conditions are closely monitored under the supervision of intensive care nephrologists.

The major clinical concerns during CRRT deal with mass balance of electrolytes and fluid during the treatment and to maintain these electrolyte concentrations at physiological concentrations. Since these concerns are reported on extensively in literature (for CRRT fluids in general) with respect to homeostasis of phosphate during CRRT, no clinical trial is needed for Phoxilium.

### **Clinical safety**

CRRT is a treatment designed for critically ill, hospitalized patients whose ARF typically occurs in the setting of multi-organ failure. CRRT as well as phosphate supplementation are well established in the literature for more than 10 years. CRRT is considered to be a safe, manageable procedure in the ICU setting and, with respect to attribution of adverse events, it is very difficult to differentiate those related to the CRRT procedure from those related either to the co-morbid conditions or to therapies directed at these co-morbid conditions. Furthermore it is also very difficult to separate the cause of adverse events related to the procedure (continuous arteriovenous haemofiltration (CAVH), CVVH, etc) from those potentially related to the solutions used for this procedure.

Safety is, however, well established for more than ten years in the literature in various conditions.

*Adverse Events*

In this ARF patient population, the mortality rate is typically high and can be predicted using APACHE II scores. The expected mortality rate in this patient population is usually over 50%. Regarding less severe adverse events, a study by Ronco et al (2000) reported the incidence of bleeding, repeated filter clotting, vascular access malfunction, and fluid balance errors as 5%, 2%, 11%, and 6%, respectively. These figures are from the largest haemofiltration study in which lactate-containing replacement solutions were used and ultrafiltration doses were compared. Filter clotting and vascular access malfunction should be regarded as adverse events related to the technique and not the electrolyte content of the solution. In smaller studies, a direct comparison between lactate- and bicarbonate-buffered solutions demonstrated a significant reduction in cardiovascular events with bicarbonate-buffered solutions (Barenbrock et al, 2000). Electrolyte disturbances and inadequate control of azotemia are related both to the renal replacement therapy and the underlying disease processes. These clinical problems can be managed either by increasing the therapy dose (e.g., ultrafiltration rate in CVVH) and/or by switching between different formulations of Hemosol/Primasol to correct imbalances. Frequent plasma sampling is required to adequately monitor these parameters.

There is no indication from studies on IV phosphate supplementation that there are specific risks related to this treatment except in two studies with reduction in ionized calcium blood concentration.

*Intrinsic factors*

Age obviously is an important determinant of survival in ICU patients. There are elderly patients in most studies but no specific trial conducted in this population. There are three studies of haemofiltration available in children from birth to eighteen years of age.

*Extrinsic Factors*

As already reported, factors extrinsic to the patient and the solution influence patient's safety but should not interfere with the safety of the solution used. These factors include local medical practices, specific CRRT modality, and patient monitoring.

*Drug Interactions*

With respect to the administration of drugs to the patient during CRRT, the physician must take into consideration whether or not significant amounts of the drugs are removed by convection or diffusion across the HD, HF, or HDF membrane during the procedure with appropriate dose adjustment as needed.

*Use in Pregnancy and Lactation*

The Hemosol/Primasol and Phoxilium solutions are formulated from normal physiological electrolytes, buffers, glucose, and water, all of which are naturally occurring molecules in the human body, therefore, there are no specific additional risks anticipated in this patient population beyond those originating from the underlying disease.

*Overdose*

The widely accepted definition of CRRT dose is an index that is proportional to uremic solute removal. Therefore, effluent flow rate is typically used to assess therapy dose. In this regard, the term "overdose" does not apply to excessive removal of endogenous toxins as this phenomenon per se is not recognized clinically. However, "overdose" with respect to excessive electrolyte/fluid addition or depletion can occur. This occurrence can be managed by changes in the flow rates of replacement fluid or dialysate, or by changes in the concentrations of solute constituents in these fluids. Moreover, this type of complication can be readily prevented by close monitoring of the patient's volume and biochemical status.

*Drug Abuse*

Drug abuse is not anticipated due to the mode of therapy.

*Withdrawal and Rebound*

Withdrawal and rebound phenomenon have not been noted in any of the publications.

*Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability*

Not applicable.

*Post marketing data*

Hemosol B0 (MRP SE/H/171/001 concluded 4 May 1999) and Primasol 2 and 4 mmol/l Potassium (MRP FR/H/226/001-002 concluded 2 April 2003) are currently being marketed in Europe and Canada (only for HD). Pharmacovigilance of these products did not reveal any adverse events related to their use during these treatments.

Risk management plan

The applicant stated to have already similar products currently on the market, e.g. Hemosol B0 (MRP SE/H/171/001) and Primasol 2 and 4 mmol/l Potassium (MRP FR/H/226/001-002) in Europe and Canada (only for HD), for which there have been no safety concerns at all. Therefore there should be no non-clinical or clinical safety concerns for Phoxilium and there is no need for a Risk Management Plan.

Pharmacovigilance system

A statement signed by the MAH and the qualified person for pharmacovigilance (QPPV) was provided, indicating that the MAH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

The following procedures documented in writing are, however, missing in the current documentation:

- Signal generation and review
- Benefit/risk assessment
- Notifying competent authorities and health professionals of changes to the benefit/risk balance
- Interaction between safety issues and product information
- Handling of urgent safety restrictions and safety variations
- Meeting commitments to competent authorities in relation to a marketing authorisation.

The MAH committed to ensure that the pharmacovigilance system will be complete, in place and functioning before Phoxilium 1.2 mmol/l phosphate is placed on the market.

**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. A cohort of 10 participants was recruited of sufficiently diverse demographic and sociologic criteria. Twelve specific questions with regard to the PIL were asked in two stages. The interviews were well-organised.

The results per stage focused upon the questions not found and/or answered correctly. For stage one this was one question and for stage two three questions. A number of changes were made to the PIL.

The PIL successfully passed in both stages. The user test showed that the leaflet enabled 90% of participants to find, and 90% of those to express in their own words each piece of information tested.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted dossier and further literature, Phoxilium 1.2 mmol/l phosphate solution for haemodialysis/haemofiltration, can be considered effective for use in a "post-acute" phase of CRRT therapy in critically ill patients with ARF when pH and kalaemia have been restored to normal and when the patient needs phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT. Its use can thus be considered well established in the literature for this indication. The chemical-pharmaceutical documentation in relation to the proposed product(s) is of sufficient high quality in view of the present European regulatory requirements.

CRRT as well as phosphate supplementation is well established in the literature for more than 10 years. Safety is well established in the literature in various conditions.

The SPC has been brought in line with the approved Dutch SPC of Priskasol 2 mmol/l potassium (NL Licence RVG 28876).

The Board followed the advice of the assessors.

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, have granted a marketing authorisation. The decentralised procedure was finished on 5 February 2009. Phoxilium 1.2 mmol/l phosphate solution for haemodialysis/haemofiltration was authorised in the Netherlands on 19 August 2009.

The proposed Harmonized Birth Date is the date of conclusion of the Decentralised Procedure, i.e. 5 February 2009, and the first Data Lock Point 6 months after this, i.e. August 2009. Subsequently, the first PSUR will cover the period from February 2009 to August 2009.

The date for the first renewal will be: 5 February 2014.

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

#### Quality - active substance

- The MAH will have the drug substances retested after one year from the internal approval date of the substance. In case the retest date given by the supplier falls before the internal retest period, the retest date taken in consideration is that of the supplier.

#### Pharmacovigilance System

- The MAH committed to ensure that the pharmacovigilance system will be complete, in place and functioning before Phoxilium 1.2 mmol/l phosphate is placed on the market.



## List of abbreviations

ARF	Acute Renal Failure
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CAPD	Continuous Ambulatory Peritoneal Dialysis
CAVH	Continuous Arteriovenous Haemofiltration
CRRT	Continuous Renal Replacement Therapy
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
CVVH	Continuous Venovenous Haemofiltration
CVVHD	Continuous Venovenous Haemodialysis
CVVHDF	Continuous Venovenous Haemodiafiltration
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ESRD	End-stage Renal Disease
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HD	Haemodialysis
HDF	Haemodiafiltration
HF	Haemofiltration
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
IHD	Intermittent Haemodialysis
IT	Intermittent Treatment
IV	Intravenous
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
RRT	Renal Replacement Therapy
SD	Standard Deviation
SLED	Sustained Low-efficiency Dialysis
SPC	Summary of Product Characteristics
t <sub>½</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States



## References

- Barenbrock M., Hausberg M., Matzkies F., de la Motte S., Schaefer R. M. *Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients* Kidney International; Vol. 58 2000: 1751-1757
- Bellomo R, Colman P, Caudwell J, Boyce N, *Acute continuous hemofiltration with dialysis: Effect on insulin concentrations and glycémie control in critically ill patients.* Critical Care Medicine 1992;20(12): 1672-1676
- Bellomo R, *Bench-to-bedside review: lactate and the kidney.* Crit Care 2002;6(4):322-6
- Chow MT, Chen J, Patel JS, Ali S, Noghnogh AA, Leehey DJ, Ing TS. *Use of a phosphorus-enriched dialysate to hemodialyze patients with ethylene glycol intoxication.* Int J Artif Organs. 1997 Feb;20(2): 101-4.
- Davenport A., Will E., Davison A.M. *The effect of lactate-buffered solutions on the acid-base status of patients with renal failure.* Nephrology Dialysis Transplantation 1989; 4: 800-804.
- Davenport A. *Replacement and dialysate fluids for patients with acute renal failure treated by continuous veno-venous haemofiltration and/or haemodiafiltration.* In Ronco C, Bellomo R, Brendolan A. Sepsis, Kidney and multiple organ dysfunction. Basel Karger 2004, pp.317-328
- Dolson GM. *Electrolyte abnormalities before and after the onset of acute renal failure.* Miner Electrolyte Metab. 1991; 17(2): 133-40.
- Dorval M, Pichette V, Cardinal J, Geadah D, Ouimet D, Leblanc M. *The use of an ethanol-and phosphate-enriched dialysate to maintain stable serum ethanol levels during haemodialysis for methanol intoxication.* Nephrol Dial Transplant 1999;14:1774-1777
- Heering P, Ivens K, Thümer O, Morgera S, Heintzen M, Passlick-Deetjen J, Willers R, Strauer Be, Grabensee B. *The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure.* Intensive Care Med. 25,11,1244-1251 (1999)
- Ing TS, Purandare VV, Daugirdas JT, Reid RW, Pierce JS, O'Neill CT. *Preparation of phosphate-containing dialysate for use in hemodialysis and peritoneal dialysis.* Int J Artif Organs. 1983 Nov;6(6):321-2.
- Kaye M. *Long term studies using a calcium-free dialysate.* Clin Nephrol 1993;4:221-224.
- Kohn OF, Kaplan AA. *High bicarbonate solutions in the treatment of lactic acidosis with continuous renal replacement therapy (CVVH and CVVH-D).* J. Am. Soc. Nephrol. 6, 3,495 (1995)
- Kurtin P, Kouba J. *Profound hypophosphatemia in the course of acute renal failure.* Am J Kidney Dis. 1987 Nov; 10(5):346-9.
- Lentz RD, Brown DM, Kjellstrand CM. *Treatment of severe hypophosphatemia.* Ann Intern Med. 1978 Dec;89(6):941-4.
- Morimatsu H, Uchino S, Bellomo R, Ronco C. *Continuous veno-venous hemodiafiltration or hemofiltration: impact on calcium, phosphate and magnesium concentrations,* Int J Artif Organs 2002;25(6):512-9
- Ratanarat R, Brendolan A, Volker G, Bonello M, Salvatori G, Andrikos E, Yavuz A, Crepaldi C, Ronco C. *Phosphate kinetics during different dialysis modalities.* Blood Purif 2005;23(1):83-90

Ronco C, Bellomo R., Homel P., Brendolan A., Dan M., Piccini P., La Greca G. *Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial.* The Lancet; Vol. 356, July 1, 2000: 26 -30

Tan HK, Bellomo R, M'Pisi DA, Ronco C. *Phosphatemic control during acute renal failure: intermittent hemodialysis versus continuous hemodiafiltration,* Int J Artif Organs 2001 ;24(4): 186-191

Troyanov S, Geadah D, Ghannoum M, et al. *Phosphate addition to hemodiafiltration solutions during continuous renal replacement therapy.* Intensive Care Med 2004;30:1662-1665

**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 (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier). Deletion of a supplier.	NL/H/1147/001/IA/001	IA	31-8-2009	14-9-2009	Approval	N