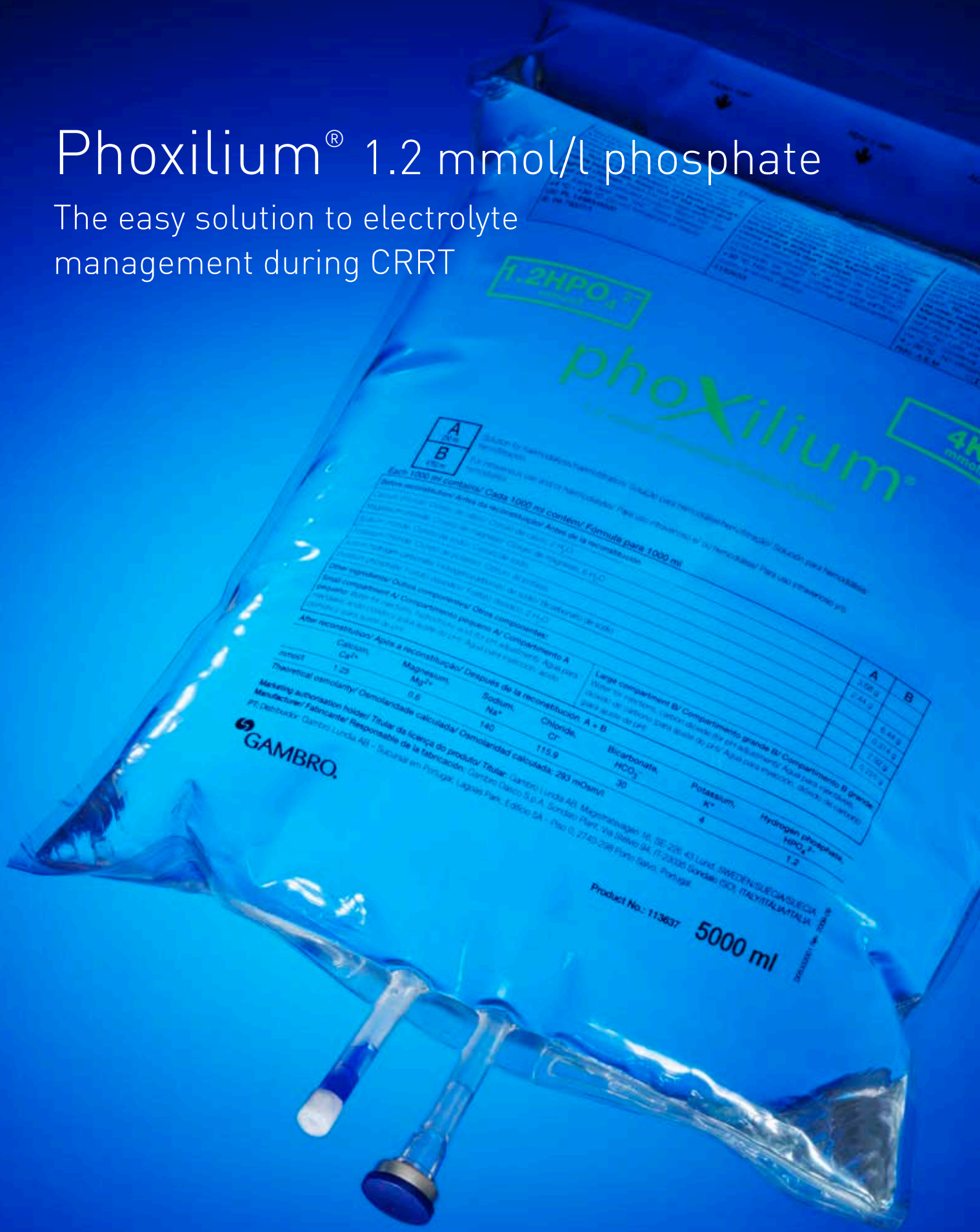


Phoxilium® 1.2 mmol/l phosphate

The easy solution to electrolyte management during CRRT



Phosphate-containing solution for
hemodialysis and hemofiltration
CVH–CVHD–CVHDF

 **GAMBRO®**

Electrolyte management in the ICU

Incidence of electrolyte disorders during CRRT

Continuous Renal Replacement Therapy (CRRT) presents several advantages over intermittent blood purification techniques, including better hemodynamic tolerability, more efficient solute clearance, better control of intravascular volume, and better clearance of middle and large molecular weight molecules.¹

However, treatment-induced complications such as electrolyte disturbances may occur if treatment is performed for a prolonged time period. Key electrolytes (e.g. phosphate, potassium, magnesium) are the most affected and often require targeted supplementation to maintain a physiological level in the patients.

For example, landmark studies^{2,3} have reported a high incidence of hypophosphatemia and hypokalemia that can affect up to 60% of renal replacement treatments in acute kidney injury patients (Table 1). Studies²⁻⁶ also demonstrate that the incidence of electrolyte disturbances is correlated with treatment parameters and patient characteristics (Table 2).

Table 1: Incidence of hypophosphatemia and hypokalemia in the VA/NIH Acute Renal Failure Trial Network study² (n=1124 patients) and RENAL study³ (n=1508 patients).

Events	Incidence* [min-max %]	
	VA/NIH ATN	RENAL
Hypophosphatemia	10.9–17.6	54.0–65.1
Hypokalemia	4.5–7.5	23.4–24.4

*Depending on different intensity of therapy performed.

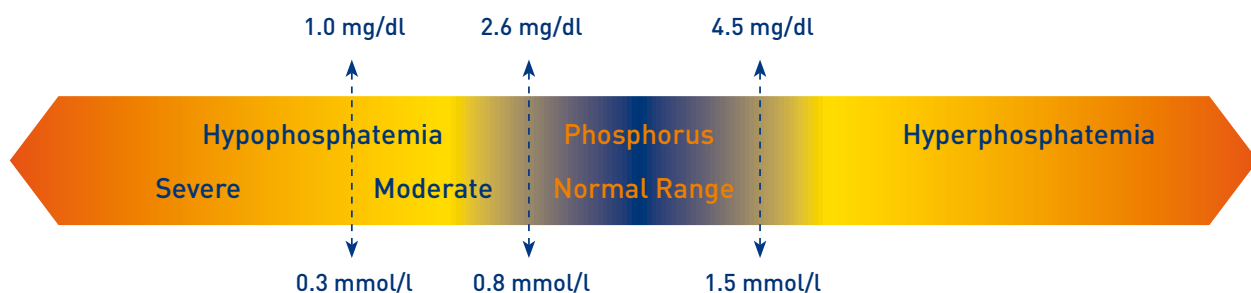
Table 2: Main factors affecting electrolyte disturbances during renal replacement therapy (RRT)²⁻⁶

Intensity of RRT
Duration of RRT
Treatment modality
Filter surface area
Age of patients

Phosphate: the most abundant intracellular anion

(Turn to page 6 to learn more about the importance of phosphorus in the body)

Figure 1: Plasma phosphorus concentration (measured as the inorganic fraction of phosphate):



Hypophosphatemia: a common complication in CRRT

Although hyperphosphatemia is frequent in acute renal failure, treatment-induced hypophosphatemia may occur when phosphorus intake is poor or in situations such as respiratory alkalosis or refeeding syndrome that induce intracellular shifts of phosphorus.

Most of the clinical manifestations of hypophosphatemia result from a decreased availability of intracellular ATP and impaired oxygen delivery to tissues.⁹ They include:^{7, 10, 11}

- Respiratory muscle failure with pulmonary insufficiency
- Arrhythmia, heart failure
- Vasodilation
- Rhabdomyolysis
- Hemolysis
- Platelet and leukocyte dysfunction
- Convulsive seizures

Studies report that a rapid correction of hypophosphatemia in surgical intensive care patients and septic shock patients significantly improves patient outcomes and reverses hypophosphatemia-induced alterations.^{12, 13}

Treatment of electrolyte disturbances

- Intravenous infusion of electrolyte solutions
- Supplementation via nutrition (nasogastric tube/TPN)
- Addition of electrolytes in replacement and/or dialysate solution

All these time consuming-procedures commit nurses and physicians to additional workload in their daily practice of CRRT. Furthermore, the addition of electrolytes directly into the bag may increase the risk of salts precipitation in the solution and induce potential complications for the patient.



Phoxilium solution—the clinical and open

An innovative pre-formulated solution from Gambro

Table 3: Composition of the Phoxilium solution

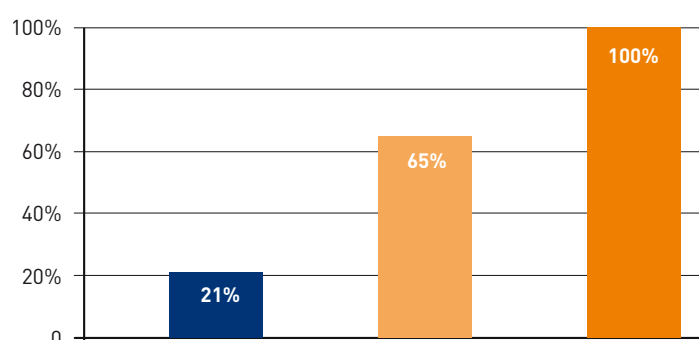
mmol/l	Phoxilium 1.2 mmol/l phosphate		Plasma ¹⁵
Bicarbonate HCO_3^-	30	Recommended concentration to maintain normal acid base balance ¹⁴ when pH has been restored to normal	22–26
Hydrogen phosphate HPO_4^{2-}	1.2	Suitable concentration to effectively correct hypophosphatemia ¹⁰	0.8–1.5
Sodium Na^+	140	Normal plasma sodium concentration	135–145
Potassium K^+	4	Normal plasma potassium concentration	3.5–5.0
Calcium Ca^{2+}	1.25	Normal plasma free ionized calcium concentration	1.14–1.30*
Magnesium Mg^{2+}	0.6	Normal plasma free ionized magnesium concentration	0.45–0.6*
Chloride Cl^-	116	Adjusted to electroneutrality	100–108

* The values of Ca^{2+} and Mg^{2+} include only the ionized (unbound) form of these ions.

Clinical evidence: use of Phoxilium solution prevents hypophosphatemia during CRRT¹⁶

In an abstract published by Broman & al.,¹⁶ the authors concluded that the use of Phoxilium solution is safe and reduces the variability of the serum phosphate level during CRRT as well as the incidence of hypophosphatemia. The study included a total of 42 critically ill patients with acute renal failure, treated with CVVHDF, and divided into three groups (Figure 2). Other electrolytes (Ca^{2+} , Mg^{2+} , K^+) as well as pH, pCO_2 and bicarbonate remained unchanged throughout the study.

Figure 2: Percentage of patients without hypophosphatemia events



Replacement solution	Bicarbonate*	Bicarbonate*	Phoxilium**
Dialysate solution	Bicarbonate*	Phoxilium**	Phoxilium**

* Bicarbonate-based solution without phosphate ** Phoxilium 1.2 mmol/l phosphate

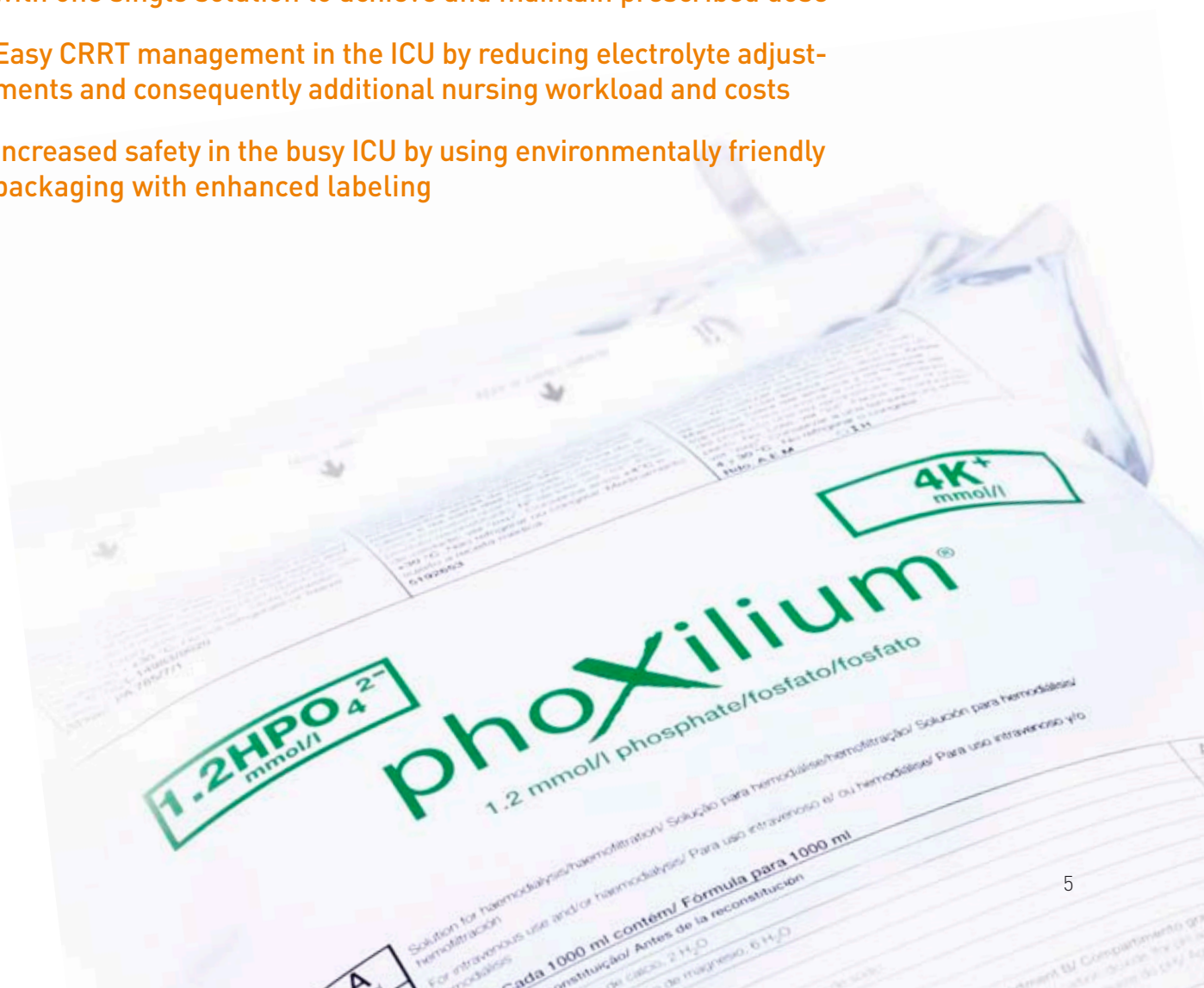
rational advantages

Phoxilium: a dialysate and replacement solution for CVVH, CVVHD and CVVHDF

Because both the dose and the treatment modality matter in CRRT, Phoxilium solution can be used either as dialysate in diffusive therapies (CVVHD & CVVHDF) or as replacement solution in convective modalities (CVVH & CVVHDF).

Advantages of Phoxilium solution in your daily practice of CRRT:

- **Prevention of electrolyte disorders and maintenance of acid base balance during prolonged CRRT**
- **Simplification of electrolyte control by using one solution with all key electrolytes at physiological level**
- **Possibility to perform both diffusive and convective therapies with one single solution to achieve and maintain prescribed dose**
- **Easy CRRT management in the ICU by reducing electrolyte adjustments and consequently additional nursing workload and costs**
- **Increased safety in the busy ICU by using environmentally friendly packaging with enhanced labeling**



Further reading

Phosphorus: an essential constituent of all body tissues ...

Around 85% of phosphorus in the body is found in the bones and teeth, 14% in the cells, and less than 1% in the extracellular fluid. It exists almost exclusively in the form of phosphate.

As phosphate is the most important intracellular anion, under certain acute conditions it may shift into or out of the cell, causing dramatic changes in plasma phosphorus concentration.⁷

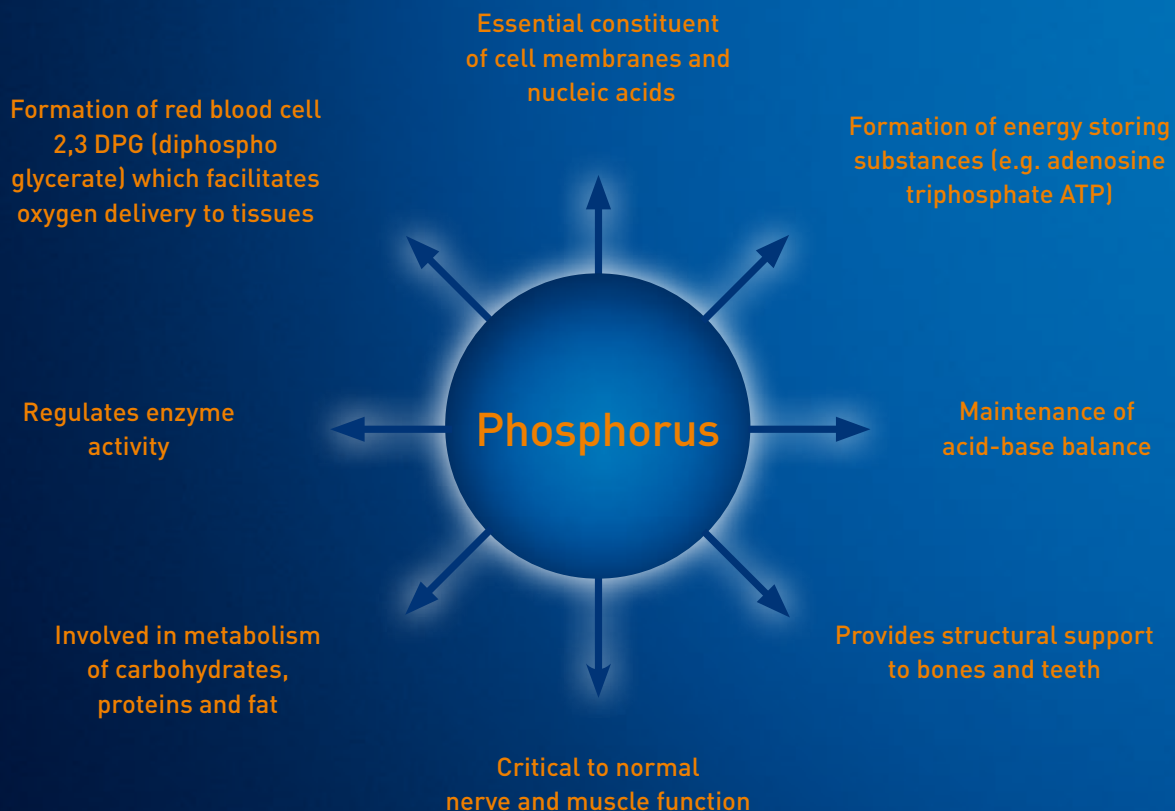


Cells 14%

Bones and teeth 85%

Extracellular fluid 1%

... which is involved in a wide variety of metabolic reactions and vital functions:^{7, 8}



Summary of Product Characteristics

Phoxilium 1.2 mmol/l phosphate. Solution for haemodialysis and haemofiltration.

Composition: Phoxilium replacement and dialysate solution is packaged in a two-compartment bag. The final reconstituted solution is obtained after breaking the peel seal and mixing both solutions. Before reconstitution, 1000 ml of solution in the small compartment (A) contains: calcium chloride ($2\text{ H}_2\text{O}$) 3.68 g, magnesium chloride ($6\text{ H}_2\text{O}$) 2.44 g. Before reconstitution, 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 ($2\text{ H}_2\text{O}$) 0.225 g. After reconstitution, see product composition table in the brochure. Each litre of the final reconstituted solution corresponds to 50 ml of solution A and 950 ml of solution B. Theoretical osmolarity: 293 mOsm/l. **Excipients:** small compartment A: water for injections, hydrochloric acid. Large compartment B: water for injections, carbon dioxide. **Indications:** Phoxilium is used 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. **Posology and method of administration:** the volume of Phoxilium used will depend on the clinical condition of the patient and the targeted fluid balance. The dose volume is therefore at the discretion and prescription of the responsible physician. The range of flow rates for the replacement solution in haemofiltration and haemodiafiltration are: adult and adolescents: 500–3000 ml/hour; children: 15–35 ml/kg/hour. The range of flow rates for the dialysis solution (dialysate) in continuous haemodialysis and continuous haemodiafiltration are: adult and adolescents: 500–2500 ml/hour; children: 15–30 ml/kg/hour. Commonly used flow rates in adults are approximately 2000 ml/h which correspond to a daily replacement fluid volume of approximately 48 l. Intravenous use and for haemodialysis. Phoxilium, when used as a replacement solution is administered into the extracorporeal circuit before (pre-dilution) or after the haemofilter or haemodiafilter (post-dilution). **Contraindications:** solution dependent contraindications: hyperkalaemia; metabolic alkalosis; hyperphosphataemia. Haemofiltration/- dialysis dependent contraindications: renal failure with pronounced hypercatabolism, if the uraemic symptoms cannot be corrected with haemofiltration or haemodiafiltration; insufficient arterial pressure in the vascular access; systemic anticoagulation if there is a high risk of haemorrhage. Special warnings and precautions for use: the solution shall be used only by, or under the direction of, a physician competent in renal failure treatments using haemofiltration and continuous haemodialysis. Check to make sure that the solutions are clear and that all seals are intact before mixing. Carefully follow the Phoxilium Instructions for Use. Solution A must be mixed with solution B before use to obtain the reconstituted solution suitable for haemofiltration and continuous haemodialysis. Do not administer the solution unless it is clear. Aseptic technique must be used during connection / disconnection of the line sets to the Phoxilium container. Use only with an appropriate extra-renal replacement equipment. The heating of this solution to body temperature (37°C) must be carefully controlled. It should also be visually verified that the solution is clear and without particles prior to administration. If not, discard and do not use the solution. Haemodynamic status, fluid balance, electrolyte and acid-base balance shall be closely monitored throughout the procedure. In case of fluid imbalance (i.e. cardiac failure, head trauma, etc), the clinical condition of the patient must be carefully monitored with restoration of normal fluid balance. The use of contaminated haemofiltration and haemodialysis solution may cause sepsis and shock. **Interactions:** the blood concentration of filterable/dialysable drugs may be reduced during treatment due to their removal by the haemodialyser, haemofilter or haemodiafilter. Corresponding corrective therapy should be instituted if necessary to establish the correct doses for drugs removed during the procedures. Interactions with other medications can be avoided by correct dosage of the solution for haemofiltration and haemodialysis. The following are several examples of potential drug interactions with Phoxilium: vitamin D and medicinal products containing calcium (e.g. calcium carbonate as phosphate binder), can increase the risk of hypercalcaemia; additional sodium bicarbonate administered in the substitution fluid may increase the risk of metabolic alkalosis. **Pregnancy and lactation:** There are no documented clinical data on the use of Phoxilium in pregnant or breast-feeding women. The prescriber should consider the benefit/risk relationship before administering Phoxilium to pregnant or breast-feeding women. **Undesirable effects:** undesirable effects can result from the solution used or the treatment. Bicarbonate-buffered haemofiltration and haemodialysis solutions are generally well tolerated. There have been no reports of adverse events or undesirable effects that might possibly be associated with the bicarbonate-buffered solutions used for haemofiltration and haemodialysis. However, the following undesirable effects are conceivable: hyper- or hypohydration, electrolyte disturbances and metabolic alkalosis. Some undesirable effects such as nausea, vomiting, muscle cramps and hypotension which are related to the treatments (haemofiltration and haemodialysis) can occur. **Overdose:** overdose with Phoxilium should not occur if the procedure is carried out correctly and the fluid balance, electrolyte and acid-base balance of the patient are carefully monitored by trained medical personnel. However, overdose resulting in fluid overload can occur in patients with acute or chronic renal failure. Continuation of treatment with haemofiltration or haemodiafiltration can be used to increase the volume of fluid removal by means of ultrafiltration, to restore normal fluid and thus correct the overdose. Thus in cases of overhydration, the ultrafiltration rate of the haemofilter or haemodiafilter must be increased and the rate of administration of the replacement solution for haemofiltration or haemodiafiltration be reduced. In cases of severe dehydration during haemofiltration or haemodiafiltration it is necessary to decrease ultrafiltration and to increase the administration of replacement solution in order to restore normal fluid balance. Phoxilium overdose can lead to severe clinical condition, such as congestive heart failure, electrolyte or acid-base disturbances. **Incompatibilities:** in the absence of compatibility studies, this product must not be mixed with other medicinal products. **Storage conditions and shelf-life:** store between $+4^\circ\text{C}$ – $+30^\circ\text{C}$. Do not refrigerate or freeze. Shelf-life: 18 months. After reconstitution: chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 22°C . If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours including the duration of the treatment. **Marketing authorisation holder:** Gambro Lundia AB, Magistratsvägen 16, SE- 226 43 Lund, SWEDEN. Date: 02/2009. **DCP licence number:** NL/H/1147/01. **Marketing authorisation number:** PL 14983/0020 (United Kingdom); PA 785/7/1 (Ireland).

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