Summary of Product Characteristics

1. Name of the medicinal product

PHOXILIUM 1.2 mmol/l phosphate Solution for haemodialysis/ haemofiltration

2. Qualitative and quantitative composition

Phoxilium replacement and dialysate solution is packaged in a two-compartment bag. The final reconstituted solution is obtained after breaking the frangible pin or the peel seal and mixing both solutions.

BEFORE RECONSTITUTION
1000 ml of solution in the small compartment (A) contains:
Calcium chloride, 2 H_2O 3.68 g
Magnesium chloride, 6 H_2O 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_2O 0.225 g

AFTER RECONSTITUTION
1 000 ml of the reconstituted solution contains:

Active substances		mmol/l	mEq/l
Calcium	Ca^{2+}	1.25	2.50
Magnesium	Mg^{2+}	0.600	1.20
Sodium	Na^{+}	140.0	140.0
Chloride	Cl^{-}	115.9	115.9
Hydrogen phosphate	HPO_4^{2-}	1.20	2.40
Hydrogen carbonate	HCO_3^{-}	30.0	30.0
Potassium	K^{+}	4.00	4.00

Each litre of the final reconstituted solution corresponds to 50 ml of solution A and 950 ml of solution B.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for haemodialysis/ haemofiltration.
Before reconstitution: Clear and colourless solutions.

Theoretical osmolarity: 293 mOsm/l
pH of the reconstituted solution: 7.0 – 8.5

4. Clinical particulars

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology:

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.

Method of administration:

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).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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.

4.4 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.

Warnings:
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.

Special precautions for use:
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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Systemic exposure to phosphate-based solution for haemodialysis/haemofiltration is negligible. No effects on fertility or during pregnancy or on the breast-fed child are anticipated.
Phoxilium can be used during pregnancy and breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hemofiltrates.

ATC code: B05ZB

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 alkalising buffer.

5.2 Pharmacokinetic properties

Not relevant.

The active ingredients in Phoxilium are pharmacologically inactive and are present at concentrations similar to physiological plasma concentrations.

5.3 Preclinical safety data

No relevant data from preclinical findings. The active ingredients are pharmacologically inactive and are present at concentrations similar to physiological plasma levels.

6. Pharmaceutical particulars

6.1 List of excipients

Small compartment A:	Water for injections
	Hydrochloric acid (for pH adjustment)
Large compartment B:	Water for injections
	Carbon dioxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

6.3 Shelf-life

18 months

After reconstitution:

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 22^{o}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.

6.4 Special precautions for storage

Store between +4 ° C - +30ºC. Do not refrigerate or freeze.

For the storage condition of the reconstituted solution, see section 6.3.

6.5 Nature and contents of container

The container made in polyvinyl chloride (PVC) or polyolefin is a two-compartment bag. 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 frangible pin or a peel seal.

The large compartment B is fitted with an injection connector (or spike connector) made of polycarbonate (PC), which is closed with a rubber disc covered by a cap as well as a luer connector (PC) with a frangible pin (PC) or a valve made of silicone rubber for the connection of the bag with a suitable replacement solution line or dialysis line.

The bag is over wrapped with a transparent overwrap made of a multilayer polymer film.

Each two-compartment bag contains 5000 ml.

Package size: 2 x 5000 ml in a box.

6.6 Special precautions for disposal and other handling

The solution in the small compartment A is added to the solution in the large compartment B after breaking the frangible pin or the peel seal immediately before use. The reconstituted solution shall be clear and colourless.

A package leaflet with detailed instruction for use is enclosed in the box.

Aseptic technique shall be used throughout the handling and administration to the patient. Use only if the solution is clear and the over wrap is undamaged. All seals must be intact. If leakage is discovered, discard the solution immediately since sterility can no longer be assured.

The large compartment B is fitted with an injection port for the possible addition of other necessary drugs after reconstitution of the solution. It is the responsibility of the physician to judge the compatibility of an additive medication with Phoxilium by checking for eventual colour change and/or eventual precipitation, insoluble complexes or crystals. The Instructions for Use of the medication to be added must be consulted.

Before adding a medication, verify it is soluble and stable in water at the pH of Phoxilium (pH of reconstituted solution is 7.0 – 8.5).

Medication shall only be added to the solution under the responsibility of a physician in the following way: Remove any fluid from the injection port, hold the bag upside down, insert the drug through the injection port and mix thoroughly. **The solution must be administered immediately.**

If a frangible pin separates the two compartments of the bag and a frangible pin is located in the luer connector the following instructions for use shall be followed:

I Remove the over wrap from the bag immediately before use and discard any other packaging materials. Open the seal by breaking the frangible pin between the two compartments of the bag. The frangible pin will remain in the bag.

II Make sure all the fluid from the small compartment A is transferred into the large compartment B.

III Rinse the small compartment A **twice** by pressing the mixed solution back into the small compartment A and then back into the large compartment B.

IV When the small compartment A is empty: shake the large compartment B so that the contents mix completely. The solution is now ready for use and the bag can be hung on the equipment.

V The dialysis or replacement line may be connected to either of the two access ports.

Va If the luer access is used, using aseptic technique, remove the cap and connect the male luer lock on the dialysis or replacement line to the female luer receptor on the bag: tighten. Using both hands, break the blue frangible pin at its base, and move it back and forth. Do not use a tool. Verify that the pin is completely separated and that the fluid is flowing freely. The pin will remain in the luer port during the treatment.

Vb If the injection port is used, first remove the snap-off cap. Then introduce the spike through the rubber septum. Verify that the fluid is flowing freely.

If a frangible pin separates the two compartments of the bag and a valve is located in the luer connector the following instructions for use shall be followed:

I Remove the over wrap from the bag immediately before use and discard any other packaging materials. Open the seal by breaking the frangible pin between the two compartments of the bag. The frangible pin will remain in the bag.

II Make sure all the fluid from the small compartment A is transferred into the large compartment B.

III Rinse the small compartment A **twice** by pressing the mixed solution back into the small compartment A and then back into the large compartment B.

IV When the small compartment A is empty: shake the large compartment B so that the contents mix completely. The solution is now ready for use and the bag can be hung on the equipment.

V The dialysis or replacement line may be connected to either of the two access ports.

Va If the luer access is used, remove the cap with a twist and pull motion, and connect the male luer lock on the dialysis or replacement line to the female luer receptor on the bag using a push and twist motion. Ensure that the connection is fully seated and tighten. The connector is now open. Verify that the fluid is flowing freely.
When the dialysis or replacement line is disconnected from the luer connector, the connector will close and the flow of the solution will stop. The luer port is a needle-less and swabbable port.

Vb If the injection port is used, first remove the snap-off cap. Then introduce the spike through the rubber septum. Verify that the fluid is flowing freely.

If a peel seal separates the two compartments of the bag and a frangible pin is located in the luer connector the following instructions for use shall be followed:

I Remove the over wrap from the bag immediately before use and discard any other packaging materials. Open the seal by holding the small compartment with both hands and squeezing it until an opening is created in the peel seal between the two compartments.

II Push with both hands on the large compartment until the peel seal between the two compartments is entirely open.

III Secure complete mixing of the solution by shaking the bag gently. The solution is now ready for use, and can be hung on the equipment.

IV The dialysis or replacement line may be connected to either of the two access ports.

IVa If the luer access is used, using aseptic technique, remove the cap and connect the male luer lock on the dialysis or replacement line to the female luer receptor on the bag: tighten. Using both hands, break the blue frangible pin at its base, and move it back and forth. Do not use a tool. Verify that the pin is completely separated and that the fluid is flowing freely. The pin will remain in the luer port during the treatment.

IVb If the injection port is used, first remove the snap-off cap. Then introduce the spike through the rubber septum. Verify that the fluid is flowing freely.

If a peel seal separates the two compartments of the bag and a valve is located in the luer connector the following instructions for use shall be followed:

I Remove the over wrap from the bag immediately before use and discard any other packaging materials. Open the seal by holding the small compartment with both hands and squeezing it until an opening is created in the peel seal between the two compartments.

II Push with both hands on the large compartment until the peel seal between the two compartments is entirely open.

III Secure complete mixing of the solution by shaking the bag gently. The solution is now ready for use, and can be hung on the equipment.

IV The dialysis or replacement line may be connected to either of the two access ports.

IVa If the luer access is used, remove the cap with a twist and pull motion, and connect the male luer lock on the dialysis or replacement line to the female luer receptor on the bag using a push and twist motion. Ensure that the connection is fully seated and tighten. The connector is now open. Verify that the fluid is flowing freely.

When the dialysis or replacement line is disconnected from the luer connector, the connector will close and the flow of the solution will stop. The luer port is a needle-less and swabbable port.

IVb If the injection port is used, first remove the snap-off cap. Then introduce the spike through the rubber septum. Verify that the fluid is flowing freely

The reconstituted solution shall be used immediately. If not used immediately, the reconstituted solution should be used within 24 hours including the duration of the treatment after addition of the solution A to solution B.

The reconstituted solution is for single use only.

Discard any unused solution immediately after use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Gambro Lundia AB
Magistratsvägen 16
SE- 226 43 Lund
SWEDEN

8. Marketing authorisation number(s)

To be completed nationally

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: DD month YYYY

Date of latest renewal: DD month YYYY

10. Date of revision of the text

DD/YYYY

To be completed nationally