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 is presented 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
1000 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 1000ml 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.
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 and rate at which Phoxilium is administered depends on the blood concentration of phosphate and other electrolytes, acid–base balance, fluid balance and overall clinical condition of the patient. The volume of replacement solution and/or dialysate to be administered will also depend on the desired intensity (dose) of the treatment. Administration (dose, infusion rate and cumulative volume) of Phoxilium should only be established by a physician experienced in critical care medicine and CRRT (Continuous Renal Replacement Therapy).

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: 500 - 3000 ml/hour

The range of flow rates for the dialysate in continuous haemodialysis and continuous haemodiafiltration are:
Adult: 500 - 2500 ml/hour

Commonly used combined total flow rates for CRRT (dialysate and replacement solutions) in adults are approximately 2000 to 2500 ml/h which correspond to a daily fluid volume of approximately 48 to 60 l.

Paediatric population:

In children from neonates to adolescents to 18 years, the range of flow rates used as substitution solution in haemofiltration and haemodiafiltration and as dialysis solution (dialysate) in continuous haemodialysis and continuous haemodiafiltration are 1000 to 4000 ml/h/1.73 m^2.

For adolescents (12-18 years), the adult dose recommendation should be used when the paediatric dose is calculated to exceed the maximum adult dose.

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).
Phoxilium, when used as a dialysate, it is administered in the dialysate compartment of the extracorporeal filter separated from the blood flow by a semipermeable membrane.

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 CRRT treatments using haemofiltration, haemodiafiltration and haemodialysis.

Warnings:

Phoxilium should not be used in patients with hyperkalemia (see section 4.3). The serum potassium concentration must be monitored before and during haemofiltration and/or haemodialysis.

Because Phoxilium is a potassium-containing solution, hyperkalaemia may occur transiently after treatment is initiated. Decrease the infusion rate and confirm that the desired potassium concentration is achieved. If hyperkalaemia does not resolve, stop administration promptly.

If hyperkalaemia develops when Phoxilium is used as a dialysate, administration of a potassium-free dialysate may be necessary to increase the rate of potassium removal.

Because Phoxilium is a phosphate-containing solution, hyperphosphatemia may occur transiently after treatment is initiated. Decrease the infusion rate and confirm that the desired phosphate concentration is achieved. If hyperphosphatemia does not resolve, stop administration promptly (See Section 4.3 Contraindication).

Electrolyte and blood acid/base parameters should be monitored regularly in patients treated with Phoxilium. Phoxilium contains hydrogen phosphate, a weak acid that can influence the patient's acid/base balance. If metabolic acidosis develops or worsens during therapy with Phoxilium, the infusion rate may need to be decreased or its administration stopped.

Because Phoxilium contains no glucose, administration may lead to hypoglycaemia. Blood glucose levels should be monitored regularly in diabetic patients (including careful consideration of patients receiving insulin or other glucose lowering medications), but also considered in non-diabetic patients, e.g. risk for silent hypoglycemia during the procedure. If hypoglycaemia develops, use of a glucose-containing solution should be considered. Other corrective measures may be necessary to maintain desired glycaemic control.

The instructions for use (see section 6.6) must be strictly followed.
The solutions in the two compartments must be mixed before use.
Use of a contaminated solution may cause sepsis and shock.

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 extracorporal renal replacement equipment.

Special precautions for use:
Phoxilium may be warmed to 37 °C to enhance patient comfort. Warming of the solution prior to use should be done before reconstitution with dry heat only. Solutions should not be heated in water or in a microwave oven. Phoxilium should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

Haemodynamic status, fluid balance, electrolyte and acid-base balance shall be closely monitored throughout the procedure including all fluid inputs and outputs, even those not directly related to CRRT.

In case of hypervolaemia, the net ultrafiltration rate prescribed for the CRRT device can be increased and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be reduced.

In case of hypovolaemia, the net ultrafiltration rate prescribed for the CRRT device can be reduced and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be increased.

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 treatment.
Interactions with other medications can be avoided by correct dosage of the solution for haemofiltration and haemodialysis.

The following are examples of potential drug interactions with Phoxilium:
• Additional sources of phosphate (e.g., hyperalimentation fluid) may influence serum phosphate concentration and may increase the risk of hyperphosphatemia,
• Vitamin D and other vitamin D analogues, as well as medicinal products containing calcium (e.g. calcium chloride or calcium gluconate used for maintenance of calcium homeostasis in CRRT patients receiving citrate anticoagulation) can increase the risk of hypercalcaemia,
• Additional sodium bicarbonate (or buffer source) contained in the CRRT fluids or in other fluids may increase the risk of metabolic alkalosis.
• When citrate is used as an anticoagulant, it contributes to the overall buffer load and can reduce plasma calcium levels.

4.6 Fertility, pregnancy and lactation

Fertility
No effects on fertility are anticipated, since calcium, sodium, potassium, magnesium, chloride, hydrogen phosphate and hydrogen carbonate are normal constituents of the body.

Pregnancy and lactation
There are no documented clinical data on the use of Phoxilium during pregnancy and lactation. Phoxilium should only be administered to pregnant and lactating women if clearly needed.

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.

The following undesirable effects have been reported from post-marketing experience. The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies cannot be estimated from the available data.

MedDra System Organ Class	Preferred Term	Frequency
Metabolism and nutrition disorders	Electrolyte imbalances, e.g.:, hyperphosphataemia	not known
	Fluid imbalance, e.g.: hypervolaemia, hypovolaemia	not known
	Acid-base balance disorders, e.g. metabolic acidosis, metabolic alkalosis	not known
Vascular disorder	Hypotension*	not known

Gastrointestinal disorder	Nausea*	not known
	Vomiting*	not known
Musculoskeletal and connective tissue disorders	Muscle cramps*	not known

* undesirable effects related generally to dialysis treatments.

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:

HPRA Pharmacovigilance, Earlsfort Terrace, IRE – Dublin 2.
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie

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 is carefully monitored by trained medical personnel.
However, Phoxilium overdose can lead to severe clinical conditions, such as congestive heart failure, electrolyte or acid-base disturbances.

If hypervolaemia or hypovolaemia occur, instruction for handling of hypervolaemia or hypovolaemia in section 4.4 must be strictly followed.
If metabolic acidosis and/or hyperphosphatemia occur, stop administration promptly. There is no specific antidote for overdose. The risk can be minimized by close monitoring during treatment (see section 4.3 and 4.4).

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 dialysate 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 medicinal 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°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 overwrap is undamaged, all seals are intact, frangible pin or peel seal is not broken, and the solution is clear. Press bag firmly to test for any leakage. 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 user to judge the compatibility of an additive medication with Phoxilium by checking for eventual colour change and/or eventual precipitation, insoluble complexes or crystals. Before adding a medication, verify if it is soluble and stable in this medicine and that the pH range of Phoxilium is appropriate (pH of reconstituted solution is 7.0–8.5).Additives may be incompatible. The Instructions for Use of the medication to be added must be consulted.

Remove any fluid from the injection port, hold the bag upside down, insert the drug through the injection port and mix thoroughly. The introduction and mixing of additives must always be performed prior to connecting the solution bag to the extracorporeal circuit. **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 dialysate 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 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

Vantive Belgium SRL
Boulevard D'Angleterre 2
Braine-L'Alleud
1420

Belgium

8 MARKETING AUTHORISATION NUMBER

PA25288/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2009
Date of last renewal: 5th May 2013

10 DATE OF REVISION OF THE TEXT

November 2024