SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Biphozyl Solution for haemodialysis / haemofiltration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Before reconstitution
Composition in the small compartment:

Magnesium chloride hexahydrate	3.05 g/l

Composition in the large compartment:

Sodium chloride	7.01 g/l
Sodium hydrogen carbonate	2.12 g/l
Potassium chloride	0.314 g/l
Disodium phosphate dihydrate	0.187 g/l

After reconstitution
Composition of the reconstituted solution:

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for haemodialysis / haemofiltration
Clear and colourless solution

Theoretical osmolarity: 290 mOsm/l
pH = 7.0 – 8.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Biphozyl is used as replacement solution and as dialysate for treatment of acute kidney injury during continuous renal replacement therapy (CRRT). Biphozyl is particularly used in a post-acute phase after initiation of renal replacement therapy when pH potassium and phosphate concentration have returned to normal or when the patients need phosphate supplementation for loss of phosphate in the ultrafiltrate or to the dialysate during CRRT.

Biphozyl is also used when other buffer sources are available as well as during regional citrate anticoagulation.
Moreover, Biphozyl is used in patients with hypercalcaemia.
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Biphozyl may also be used in cases of drug poisoning or intoxications when the substances are dialysable or filterable.

4.2 Posology and method of administration

Posology

The volume and rate at which Biphozyl 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 Biphozyl should only be established by a physician experienced in critical care medicine and CRRT (Continuous Renal Replacement Therapy).

The range of flow rates when used as replacement solution in haemofiltration and haemodiafiltration are:
Adult: 500 - 3000 ml/h

The range of flow rates when used as dialysate in continuous haemodialysis and continuous haemodiafiltration are:
Adult: 500 - 2500 ml/h

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

Elderly patients
Adults > 65 years of age: Evidence from clinical studies and experience suggests that use in the elderly population is not associated with differences in safety or effectiveness.

Method of administration
Intravenous use and use in haemodialysis.

Biphozyl, when used as a replacement solution, is administered into the extracorporeal circuit before (pre-dilution) or after (post-dilution) the haemofilter or haemodiafilter.

Biphozyl, 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 (Special precautions for disposal and other handling).

4.3 Contraindications

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

Hypocalcaemia unless calcium is provided to the patient by other sources.

Hyperkalaemia.

Hyperphosphatemia.

4.4 Special warnings and precautions for use

The solution should be used only by, or under the direction of, a physician competent in CRRT treatments using haemofiltration, haemodiafiltration and haemodialysis.

Warnings

Biphozyl 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 Biphozyl 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 Biphozyl is used as a dialysate, administration of a potassium-free dialysate may be necessary to increase the rate of potassium removal.

Because Biphozyl 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).

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

Because Biphozyl 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.

Use only with an appropriate extracorporal renal replacement equipment.

Special precautions for use

Biphozyl is calcium free and could cause hypocalcaemia (see section 4.8). Infusion of calcium might be necessary.
Biphozyl 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. Biphozyl 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 should be closely monitored throughout the procedure including all fluid inputs and outputs, even those not directly related to CRRT.
The content of hydrogen carbonate in Biphozyl is at the lower end of the normal range for blood concentration. Biphozyl is appropriate when using citrate anticoagulation, as citrate is metabolized to hydrogen carbonate, or when CRRT has been able to restore normal pH values. Assessment of buffer needs through measurement of repeated blood acid/base parameters and review of the overall therapy is mandatory. A solution with higher hydrogen carbonate content may be required.

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. (see section 4.9)
For general therapy related precautions / contraindications see section 4.3.

4.5 Interaction with other medicinal products and other forms of interaction

The blood concentration of filterable/dialysable drugs may be reduced during the treatment due to their removal by the haemodialyser, haemofilter or haemodiafilter. Corresponding corrective therapy should be instituted if necessary to establish the desired blood concentrations for drugs removed during treatment.

Additional sources of phosphate (e.g., hyperalimentation fluid) may influence serum phosphate concentration and may increase the risk of hyperphosphatemia.

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 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 Biphozyl during pregnancy and lactation. Biphozyl should only be administered to pregnant and lactating women if clearly needed.

4.7 Effects on ability to drive and use machines

Biphozyl is not known to affect the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects can result from the Biphozyl solution used or the dialysis treatment. Special precautions for use have been described in section 4.4.

The following undesirable effects are reported from post-marketing experience. Hydrogen carbonate-buffered haemofiltration and haemodialysis solutions are generally well tolerated. 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.: hypocalcaemia, hyperkalaemia, hyperphosphataemia	not known
	Fluid imbalance, e.g.: hypervolaemia*, hypovolaemia*	not known
	Acid-base balance disorders, e.g. metabolic acidosis	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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdose of Biphozyl can lead to severe clinical condition, 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 in the event of an overdose, 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: Haemofiltrates
ATC code: B05ZB

The constituents of Biphozyl are naturally and physiologically occurring electrolytes. Sodium, potassium, magnesium, chloride and phosphate ions are present at concentrations similar to physiological levels in plasma. The concentrations of these electrolytes are the same whether the solution is used as a replacement or as a dialysate.

Sodium and potassium concentrations in the replacement solutions are kept within the normal range of serum concentration. Chloride concentration in the formulation depends on the relative amount of the other electrolytes. Hydrogen carbonate, the physiological buffer of the body, is used as an alkalizing buffer.

From a pharmacodynamic point of view, this drug product after reconstitution is pharmacologically inactive. The drug substances are normal constituents of the physiological plasma and their concentrations in the solutions are only aimed to restore or normalize the plasma acid-base and electrolyte balance. Toxic effects due the use of Biphozyl are not expected at therapeutic dose.

5.2 Pharmacokinetic properties

Sodium, potassium, magnesium, chloride and phosphate ions are present at concentrations similar to physiological levels in plasma. Absorption and distribution of the constituents of Biphozyl is determined by the patient's clinical condition, metabolic status, and residual renal function. All the ingredients are present at physiological concentrations. Additional pharmacokinetics studies are therefore not considered relevant or applicable in this scenario.

5.3 Preclinical safety data

The drug substances included are physiological components in human plasma. According to the available information and the clinical experience with these substances used in chronic treatment of renal failure or in intensive care units, no toxic effects are expected at therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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 should not be longer than 24 hours including the duration of the treatment.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Do not freeze.

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

6.5 Nature and contents of container

The container is a two-compartment bag made of a multilayer film containing polyolefins and elastomers. The 5000 ml bag is comprised of a small compartment (250 ml) and a large compartment (4750 ml). The two compartments are separated by a peel seal. The bag is fitted with an injection connector (or spike connector) made of polycarbonate (PC) and a luer connector (PC) with a valve made of silicone rubber for the connection with a suitable solution line. The bag is overwrapped with a transparent overwrap made of polymer film.
Pack size: 2 x 5000 ml in a box

6.6 Special precautions for disposal and other handling

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

Aseptic technique should be used throughout administration to the patient.
Use only if the overwrap is undamaged, all seals are intact, 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 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 determine the compatibility of an additive medication with Biphozyl by checking for possible colour change and/or possible 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 Biphozyl is appropriate (pH of reconstituted solution is 7.0–8.0). Additives may be incompatible. The instructions for use of the medication to be added must be consulted.

Mix the solution thoroughly when additives have been introduced. The introduction and mixing of additives must always be performed prior to connecting the solution bag to the extracorporeal circuit.

Remove the overwrap from the bag immediately before use.
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. Push with both hands on the large compartment until the peel seal is entirely open.
Secure complete mixing of the solution by shaking the bag gently. The solution is now ready for use, and should be used immediately.
The dialysis or replacement line may be connected to either of the two access ports. After connection verify that the fluid is flowing freely.

The reconstituted solution is for single use only. Any unused solution must be discarded.
The solution can be disposed of via wastewater without harming the environment.

7. MARKETING AUTHORISATION HOLDER

Gambro Lundia AB
Magistratsvägen 16
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

MM/YYYY