ANNEX I

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

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 dialysis solution for treatment of acute kidney injury during continuous renal replacement therapy (CRRT). Biphozyl is used in a post-acute phase after initiation of renal replacement therapy when pH, potassium and phosphate concentration have returned to normal. 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.

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 of Biphozyl to be used will depend on the clinical condition of the patient, target electrolyte and fluid balance, buffer need and other solutions that may be needed concomitantly.
The dose is therefore at the discretion and prescription of the responsible physician.

The range of flow rates when used as replacement solution in haemofiltration and haemodiafiltration are:
Adult and adolescents: 500 - 3000 ml/h
Children: 15 - 35 ml/kg/h

The range of flow rates when used as dialysis fluid (dialysate) in continuous haemodialysis and continuous haemodiafiltration are:
Adult and adolescents: 500 - 2500 ml/h
Children: 15 - 30 ml/kg/h

Commonly used flow rates in adults are approximately 2000 ml/h which correspond to a daily replacement fluid volume of approximately 20-25 ml/kg/h.

Paediatric population
Children < 16 years of age: Evidence from clinical studies and experience suggests that use in the paediatric population is not associated with differences in safety or effectiveness.

Older people
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 dialysis fluid (dialysate) it is administered in the dialysate compartment of the 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 in CRRT.

Warnings

Use only if the solution is clear and free from visible particles.

The instructions for use (see section 6.6) must be strictly followed.

The solutions in the two compartments must be mixed before use.

Use only with a dialysis machine for continuous renal replacement therapy (CRRT).

Use only if the overwrap and solution bag are undamaged. All seals must be intact. Use of a contaminated solution may cause sepsis and shock.

Incorrect use of the access ports or other restrictions to fluid flow might lead to incorrect patient weight loss and may result in machine alarms. Continuing treatment without resolving the originating cause may result in patient injury or death.

Special precautions for use

Biphozyl is calcium free and could cause hypocalcaemia (see section 4.8). Infusion of calcium might be necessary.

If heating of the solution to body temperature (+37ºC) is necessary the procedure must be carefully controlled. The product should be visually verified that the solution is clear and without particles prior to administration. If not, discard the solution.

Haemodynamic status, fluid balance, electrolyte and acid-base balance should be closely monitored throughout the procedure.

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 repeated blood pH measurement 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)

It is the responsibility of the physician to determine the compatibility of an additive medication with this medicine by checking for possible colour change and/or possible precipitation. Before adding a medication, verify if it is soluble and stable in this medicine.

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. The use of the product may result in alteration of the patient's plasma electrolyte levels. The physician must carefully consider that medicines being used by the patient may be affected by this alteration.

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 your 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 have been described in published literature (Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data):

Hydrogen carbonate-buffered haemofiltration and haemodialysis solutions are generally well tolerated. However, the following undesirable effects are conceivable:

Metabolism and nutrition disorders	
Not known	Electrolyte imbalances, e.g.: hypocalcaemia (see section 4.4), hyperkalaemia (see section 4.3), hyperphosphataemia (see section 4.3)
	Fluid imbalance, e.g.: hypervolaemia* (see section 4.4), hypovolaemia* (see section 4.4)
Vascular disorder	
Not known	Hypotension*
Gastrointestinal disorder	
Not known	Nausea*
	Vomiting*
Muscoskeletal and connective tissue disorders	
Not known	Muscle cramps*

* undesirable effects related to the dialysis treatment

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

Symptoms of overdose
Overdose of Biphozyl can lead to severe clinical condition, such as congestive heart failure, electrolyte or acid-base disturbances.

Treatment of overdose

- Hypervolaemia

Overdose resulting in fluid overload with pulmonary oedema and other signs of congestive heart failure can occur in patients with acute or chronic renal failure. Continuation of treatment with haemodialysis, haemofiltration or haemodiafiltration can be used to increase the volume of fluid removal by means of ultrafiltration, to restore normal fluid balance and thus correct the overdose.
Thus in cases 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.

- Hypovolaemia

In cases of severe hypovolaemia during haemofiltration or haemodiafiltration, 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.

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

Biphozyl is for single use only. Any unused solution must be discarded.

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 frangible pin (PC) or 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

Aseptic technique should be used throughout administration to the patient.

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.

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