Package leaflet: Information for the user

Biphozyl Solution for haemodialysis / haemofiltration
Magnesium chloride hexahydrate, Sodium chloride, Sodium hydrogen carbonate, Potassium chloride, Disodium phosphate dihydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Biphozyl is and what it is used for
2. What you need to know before you use Biphozyl
3. How to use Biphozyl
4. Possible side effects
5. How to store Biphozyl
6. Contents of the pack and other information

1. What Biphozyl is and what it is used for

This medicine is a solution for dialysis treatment (haemofiltration, haemodialysis and haemodiafiltration) which is used to remove waste products from the blood when the kidneys are not functioning. This medicine is used in hospitals during intensive care treatment using Continuous Renal Replacement Therapy (CRRT). This medicine is particularly used to treat critically ill patients with acute kidney injury having:
- a normal concentration of potassium (normal kalaemia) in the blood
- a normal pH in the blood
- a normal concentration of phosphate (normal phosphataemia) in the blood
- a high concentration of calcium (hypercalcaemia) in the blood

This medicine may also be used
- when other bicarbonate sources are available or when extracorporeal circuit is anticoagulated with citrate.
- in case of drug poisoning or intoxications with dialysable or filterable substances.

2. What you need to know before you use Biphozyl

Do not use Biphozyl in case of:
- allergy to one of the active substances or any of the other ingredients (listed in section 6)
- a low concentration of calcium (hypocalcaemia) in the blood
- a high concentration of potassium (hyperkalaemia) in the blood
- a high concentration of phosphate (hyperphosphataemia) in the blood

Warnings and precautions

Warnings
Talk to your doctor, pharmacist or nurse before using Biphozyl.

Biphozyl should not be used in patients with high blood potassium concentration. The level of your blood potassium concentration will be monitored regularly before and during treatment.

Because Biphozyl contains potassium, high blood potassium level may occur shortly after starting the treatment. Your doctor will decrease the infusion rate and confirm that the potassium concentration has returned to desired level. If the condition does not resolve, the doctor must stop the administration

immediately. The use of a potassium-free solution may be used transiently to restore your blood potassium level.

Because Biphozyl contains phosphate, high blood phosphate level may occur shortly after starting the treatment. Your doctor will decrease the infusion rate and confirm that the phosphate concentration has returned to desired level. If the condition does not resolve, the doctor must stop the administration immediately.

Because Biphozyl contains no glucose, low blood glucose level may occur during treatment. Blood glucose levels will be monitored regularly. If low blood glucose develops, your doctor may use a glucose-containing solution. Other corrective measures may be necessary to maintain desired blood glucose concentration.

Your doctor will regularly monitor electrolyte and blood acid–base parameters in patients treated with Biphozyl. Biphozyl contains hydrogen phosphate, a weak acid that can influence your acid-base balance. If a reduction of the plasma bicarbonate concentration develops or worsens during therapy with Biphozyl, your doctor will decrease the infusion rate. If the condition does not resolve, the doctor must stop the administration immediately.

The instructions for use must be strictly followed.

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

Use only with a dialysis machine for 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.

Use only with an appropriate extracorporal renal replacement equipment

Precautions
This medicine is calcium free and could cause hypocalcaemia. 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.Do not administer unless the solution is clear and the seal is intact.

Your doctor will closely monitor your haemodynamic status, fluid balance, electrolyte and acid-base balance throughout the procedure, including all fluid inputs (intravenous infusion) and outputs (urine output), even those not directly related to CRRT.

This medicine has a hydrogen carbonate content at the lower end of the normal concentration range in the blood. This is appropriate when using citrate anticoagulation, as citrate is metabolized to hydrogen carbonate, or when normal pH values have been restored. Assessment of buffer needs, through repeated measurement of blood acid/base parameter and review of the overall therapy, is mandatory. A solution with higher hydrogen carbonate content may be required.

In case of abnormally high volume of fluid in the body (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 abnormally low volume of fluid in the body (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.

Children
No specific adverse effect on children is expected when using this medicine.

Elderly patients
No specific adverse effect on elderly patients is expected when using this medicine.

Other medicines and Biphozyl
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription. This is because the concentration of other medicines may be reduced during dialysis treatment. Your doctor will decide if any changes in the dosage of your medicines should be made.

In particular, tell your doctor if you are using either of the following:
• Additional sources of phosphate (e.g. nutritional fluids); as this may increase the risk of a high concentration of phosphate in the blood *(hyperphosphatemia).*
• Sodium bicarbonate; as this may increase the risk of excess of bicarbonate in your blood *(metabolic alkalosis).*
• When citrate is used as an anticoagulant, as it can reduce plasma calcium levels.

Pregnancy, breast-feeding and fertility
Pregnancy and breast-feeding:
There is no documented clinical data on the use of this medicine during pregnancy and lactation. This medicine should only be administered to pregnant and lactating women if clearly needed.

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

Driving and using machines
This medicine is not known to affect the ability to drive or use machines.

3. How to use Biphozyl

For intravenous use and use in haemodialysis. This medicine is to be used in hospitals and administered by medical professionals only. The volume used, and therefore the dose of this medicine, will depend on your condition. The dose volume will be determined by your doctor.

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
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.

Posology
The range of flow rates when used as replacement solution in haemofiltration and haemodiafiltration are:
Adult: 500 - 3000 ml/h
Children < 18 years old: 1000 to 4000 ml/h/1.73 m^2

The range of flow rates when used as dialysate in continuous haemodialysis and continuous haemodiafiltration are:
Adult: 500 - 2500 ml/h
Children < 18 years old: 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.

Instructions for use
This medicine will be given to you in a hospital. Your doctor will know how to use it.
For instructions for use see the end of this leaflet.

If you use more of Biphozyl than you should
Contact your doctor or nurse immediately if you have taken more of this medicine than recommended in this package leaflet or than prescribed by your doctor and you feel uncomfortable.
The symptoms of overdose are tiredness, oedema or shortness of breath.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your blood tests and clinical condition will be regularly monitored by a doctor or nurse in order to find possible side effects.
Use of this solution could cause:
• Changes of levels of salts in the blood (electrolyte imbalances) such as: low calcium level (hypocalcaemia), high potassium level (hyperkalaemia) and high phosphate level (hyperphosphataemia)
• Reduction of the plasma bicarbonate concentration (metabolic acidosis)

There are also some side effects which can be caused by dialysis treatments, such as:
• Abnormally high (hypervolaemia) or low volume (hypovolaemia) of fluid in the body
• Decreased blood pressure
• Nausea, vomiting
• Muscle cramps

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Malta:
ADR Reporting Website:
www.medicinesauthority.gov.mt/adrportal

Republic of Ireland:
HPRA Pharmacovigilance, Website: www.hpra.ie’

United Kingdom:
Yellow Card Scheme
www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Biphozyl

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the packaging. The expiry date refers to the last day of that month.

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

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.

The solution can be disposed of via wastewater without harming the environment.

Do not use this medicine if you notice damage to the product or visible particles in the solution. All seals must be intact.

6. Contents of the pack and other information

What Biphozyl contains
Before reconstitution
In the small compartment, A (250 ml):

Magnesium chloride hexahydrate	3.05 g/l

In the large compartment, B (4750 ml):

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
the reconstituted solution, A+B:

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

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

The other ingredients are:
Dilute hydrochloric acid (for pH adjustment) E 507
Water for injections
Carbon dioxide (for pH adjustment) E 290

What Biphozyl looks like and contents of the pack
This medicine is a solution for haemodialysis / haemofiltration and is packed in a two-compartment bag of a multilayer film containing polyolefins and elastomers. The final solution is obtained after opening the peel seal and mixing the solutions in the small and large compartments. The solution is clear and colourless.
Each bag contains 5000 ml solution and the bag is overwrapped with a transparent film.
Each box contains two bags and one package leaflet.

Marketing Authorisation Holder
Republic of Ireland and Malta:
Baxter Holding B.V.
Kobaltweg 49
3542 CE Utrecht
Netherlands

United Kingdom:
Baxter Healthcare Ltd,
Caxton Way, Thetford,
Norfolk, IP24 3SE,
United Kingdom

Manufacturer
Bieffe Medital S.p.A.
Via Stelvio, 94
23035 Sondalo (SO)
Italy

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:
Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Northern Ireland): BIPHOZYL
Bulgaria: BIPHOZYL (Бифозил)

This leaflet was last revised in 03/2023

The following information is intended for healthcare professionals only:

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 m2.
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.

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 / Hypovolaemia
- If hypervolaemia or hypovolaemia occur, instruction for handling of hypervolaemia or hypovolaemia in Warnings (Section 2) must be strictly followed. Metabolic acidosis

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.

Preparation and/or 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 judge the compatibility of an additive medication with Biphozyl 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 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.

I 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. (See figure I. below)

II Push with both hands on the large compartment until the peel seal between the two compartments is entirely open. (See figure II. below)

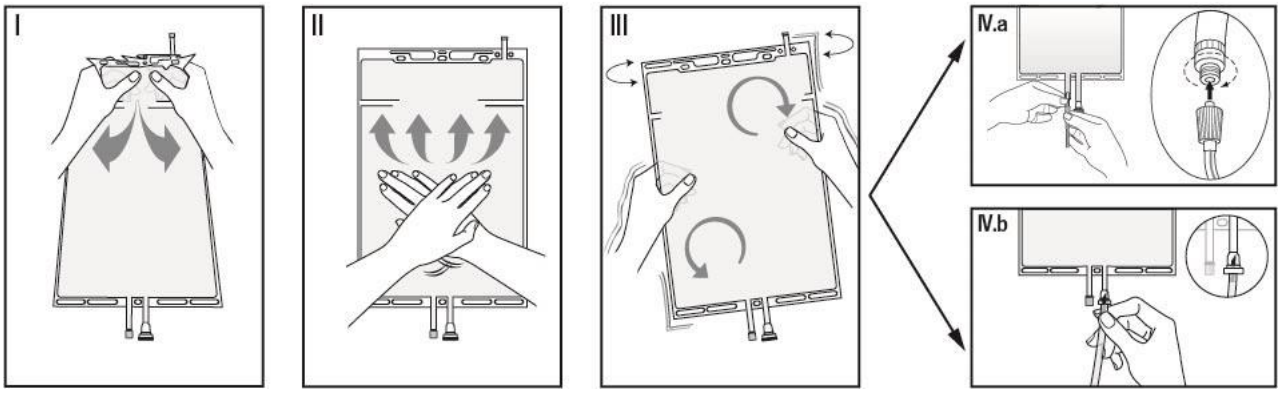
III Secure complete mixing of the solution by shaking the bag gently. The solution is now ready for use, and can be hung on the equipment. (See figure III. below)

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

IVa If the luer connector 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 connector 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. (See figure IV.a below)

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 connector (or spike connector) is used, first remove the snap-off cap. The injection port is a swabbable port. Introduce the spike through the rubber septum. Verify that the fluid is flowing freely. (See figure IV.b below)



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.