1 HEMOSOL B0 (solution, dialysis)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hemosol B0, is a solution for haemodialysis and haemofiltration consisting of a mixture of the following five active ingredients: Calcium chloride dihydrate, Magnesium chloride hexahydrate, (*S*)-Lactic acid, Sodium bicarbonate and Sodium chloride.

Hemosol B0 is contained in a two-compartment polyolefin bag containing an electrolyte solution in the small compartment (compartment A) and the buffer solution in the large compartment (compartment B).

The quantities of these active ingredients are provided in the following tables.

Before reconstitution

1000mL of electrolyte solution (small compartment A) contains: *Active substances*	
Calcium chloride dihydrate Magnesium chloride hexahydrate (S)-Lactic acid	5.145g 2.033g 5.4g
1000mL of buffer solution (large compartment B) contains: *Active substances*	
Sodium bicarbonate Sodium chloride	3.09g 6.45g

After reconstitution

The small and the large compartments are mixed to give one reconstituted solution with the following ionic composition:

1000mL of the reconstituted solution contains:			
Active substances		*mmol/L*	*mEq/L*
Sodium	Na^+	140	140
Calcium	Ca^{2+}	1.75	3.5
Magnesium	Mg^{2+}	0.5	1.0
Chloride	Cl^-	109.5	109.5
Hydrogen carbonate	HCO_3^-	32	32
Lactate		3	3

Theoretical osmolarity: 287mOsm/L.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution, dialysis.

Hemosol B0 solution is clear and colourless when reconstituted as a solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hemosol B0 is used in the treatment of renal failure, as substitution solution in haemofiltration and haemodiafiltration and as dialysis solution in continuous haemodialysis or continuous haemodiafiltration.

Hemosol B0 may also be used in case of drug poisoning with dialysable or filterable substances.

Hemosol B0 is indicated in patients who have tendency to hyperkalaemia, see section 4.4.

4.2 Dose and method of administration

Posology

Hemosol B0 is used as a substitution solution and/or dialysate. The volume of Hemosol B0 solution to be administered will depend on the intensity of the treatment performed and on the amount of solution, which has to be replaced in order to achieve the target fluid balance. The dose volume is therefore at the discretion of the responsible physician.

The rate at which Hemosol B0 is administered depends on the blood concentration of electrolytes, acid-base balance and overall clinical condition of the patient. The volume of substitution solution and/or dialysate to be administered will also depend on the desired intensity (dose) of the treatment. The solution should be prescribed and administration should be established only by a physician experienced in critical care medicine and Continuous Renal Replacement Therapies (CRRT).

If phosphate is added, phosphate up to 1.2mmol/L may be added to Hemosol B0. If potassium phosphate is added, the total potassium concentration should not exceed 4mEq/L (4mmol/L).

Hemosol B0 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.

Commonly used flow rates for the substitution solution in haemofiltration and haemodiafiltration are:

Adults and adolescents:	500 - 1500mL/hour
Neonates, infants and children:	15 - 20mL/kg/hour.

Commonly used flow rates for the dialysis solution (dialysate) in continuous haemodialysis are:

Adults and adolescents:	500 - 2000mL/hour
Neonates, infants and children:	15 - 20mL/kg/hour.

Hemosol B0 solution, when used as a substitution solution is administered into the extracorporeal circuit before (pre-dilution) or after the haemofilter (post-dilution) or haemodiafilter.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hemosol B0 may be warmed to 37°C to enhance patient comfort. Warming of Hemosol B0 prior to use should be done before reconstitution with dry heat only (e.g., heating pad, warming plate). Solutions should not be heated in water or in a microwave oven due to the potential for patient injury or discomfort. The heating of this substitution solution to body temperature (+37°C) must be carefully controlled.

Before and during treatment, haemodynamic status, fluid balance, electrolyte and acid-base balance should be closely monitored throughout the procedure. Special attention should be given to potassium levels. Phosphate substitution and potassium supplementation might be necessary. 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 substitution 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 substitution fluid and/or dialysate can be increased.

The use of contaminated haemodialysis and haemofiltration solution may cause sepsis, shock and fatal conditions.

The Hemosol B0 solution is potassium-free. Special attention should be given to potassium levels. The serum potassium concentration must be monitored before and during haemofiltration and/or haemodialysis.

Check that the solutions are clear and that all seals are intact before mixing. Carefully follow the instructions for use.

Because Hemosol B0 contains no glucose, administration of Hemosol B0 may lead to hypoglycaemia. Blood glucose levels should be monitored regularly. If hypoglycaemia develops, use of a glucose-containing solution should be considered. Other corrective measures may be necessary to maintain desired glycaemic control.

Hemosol B0 contains hydrogen carbonate (bicarbonate), and lactate (a bicarbonate precursor) which can influence the patient's acid-base balance. If metabolic alkalosis develops or worsens during therapy with Hemosol B0, the administration rate may need to be decreased, or administration stopped.

The electrolyte solution must be mixed with the buffer solution before use to obtain the final solution.

Do not administer the solution unless it is clear. Aseptic technique must be used during connection / disconnection of the line sets.

When used with a monitor, only monitors for CRRT must be used. Do not use with a haemodialysis monitor.

Paediatric use
There are no specific warnings and precautions when using this medicine for children.

There are no specific studies with Hemosol B0 solution for effects on paediatric population. Haemodynamic status, fluid balance, electrolyte and acid-base balance must be closely monitored.

Use in elderly
There are no specific studies with Hemosol B0 solution for effects on the elderly. However since the ingredients are pharmacologically inactive and present at concentrations similar to physiological plasma levels no adverse effects are expected.

Effect on laboratory tests
The effect of this medicine on laboratory tests has not been established.

4.5 Interaction with other medicines and other forms of interaction

The blood concentration of filterable/dialysable medicines may be reduced during treatment due to their removal by the extracorporeal filter. Corresponding corrective therapy should be instituted if necessary to establish the desired blood concentrations for medicines removed during treatment. When citrate is used as an anticoagulant, it contributes to the overall buffer load and can reduce plasma calcium levels.

Interactions with other medications due to electrolyte and/or acid-base imbalances can be avoided by correct dosage of the solution for haemofiltration and haemodialysis and precise monitoring.

However, the following interactions are conceivable:

- The risk of digitalis-induced cardiac arrhythmia is increased during hypokalaemia;
- Vitamin D and other Vitamin D analogues, as well as medicinal products containing calcium, (e.g. calcium chloride, calcium carbonate as phosphate binder 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 administered during therapy may increase the risk of metabolic alkalosis.

4.6 Fertility, pregnancy and lactation

Fertility

There are no specific studies with Hemosol B0 solution for effects on fertility. However since the component electrolytes are present at concentrations similar to physiological plasma levels no adverse effects on fertility are anticipated.

Pregnancy

There is no report, or adequate data on the use of Hemosol B0 solution during pregnancy but literature on renal replacement therapy during acute kidney injury does not suggest risks associated with the solution. The prescriber should consider the benefit/risk relationship before administering Hemosol B0 solution to pregnant women.

Breast-feeding

There is no report, or adequate data, on use of Hemosol B0 solution during lactation but literature on renal replacement therapy during acute kidney injury does not suggest risks associated with the solution. The prescriber should consider the benefit/risk relationship before administering Hemosol B0 solution to breast-feeding women.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Some adverse effects related to haemofiltration and haemodialysis treatment can occur, such as nausea, vomiting, muscle cramps and hypotension.

Electrolyte disturbances may occur. Special attention must be taken for patients with hypokalaemia as this solution is potassium-free, see section 4.4.

Adverse effects from clinical trials (RENAL study)

- Hypophosphataemia
- Hypokalaemia
- Arrhythmia
- Disequilibrium.

Post- marketing adverse effects

- Metabolism and nutrition disorders: hypophosphataemia.

Other (class) adverse effects

- Hypotension
- Acid-base balance disorders
- Electrolyte imbalance
- Fluid imbalance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdose with Hemosol B0 substitution fluid 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. However, overdose will result in fluid overload in patients with renal failure.

Continuation of treatment with haemofiltration will remove excess fluid and electrolytes. 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. In the 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.

Overdose could lead to severe consequences, such as congestive heart failure, electrolyte or acid-base disturbances.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Haemofiltrates.
ATC code: B05ZB.

Hemosol B0 solution contains sodium, calcium, magnesium and chloride ions at concentrations similar to physiological levels in plasma. The electrolytes Na^+, Mg^{2+}, Ca^{2+}, Cl^-, bicarbonate and lactate are essential for the maintenance and correction of fluids and electrolyte homeostasis (blood volume, osmotic equilibrium, acid-base balance). The pharmacodynamic effects of the haemodialysis and haemofiltration solution result from the additive physiological effects of the single components.

During continuous haemofiltration water and solutes such as uremic toxins, electrolytes, and bicarbonate are removed from the blood by ultrafiltration. The ultrafiltrate is replaced by a substitution solution (Hemosol B0), with a balanced electrolyte and buffer composition.

The ready-to-use Hemosol B0 solution is a bicarbonate-buffered substitution solution for intravenous administration for the treatment of acute renal failure, of any origin, by continuous haemofiltration.

Physiochemical properties
Calcium chloride dihydrate
Molecular formula: $CaCl_2 \cdot 2H_2O$
Molecular Weight: 147.0g/mol
CAS No.: 10035-04-8
Appearance: a white or almost white crystalline powder.
Solubility: freely soluble in water, and soluble in ethanol (96%).

Magnesium chloride hexahydrate
Molecular formula: $MgCl_2 \cdot 6H_2O$
Molecular Weight: 203.3g/mol
CAS No.: 7791-18-6
Appearance: colourless crystals.
Solubility: very soluble in water, and freely soluble in ethanol (96%).

(S)-Lactic acid
Molecular formula: $C_3H_6O_3$
Molecular Weight: 90.1g/mol
CAS No.: 77-33-4
Appearance: colourless or slightly yellow, syrupy liquid.
Solubility: miscible with water and with ethanol (96%).

Sodium Bicarbonate
Molecular formula: $NaHCO_3$
Molecular Weight: 84.0g/mol
CAS No.: 144-55-8
Appearance: a white or almost white, crystalline powder.
Solubility: soluble in water, and practically insoluble in ethanol (96%).

Sodium chloride
Molecular formula: NaCl
Molecular Weight: 58.44g/mol
CAS No.: 7647-14-5
Appearance: a white or almost white crystalline powder or is presented as colourless crystals, white or almost white pearls.
Solubility: freely soluble in water, and practically insoluble in ethanol.

Clinical trials
Hemosol B0 has had a long use as a bicarbonate-buffered solution in renal replacement therapy. No clinical trials were conducted during the development of Hemosol B0.

In the RENAL Study; NEJM 2009 361; 1627 - 1638 Hemosol B0 solution was used as replacement and dialysate fluid in both study groups (higher and lower intensity CRRT). This study was a multicentre, randomised trial to compare the effect of CRRT, delivered at two different levels of intensity, on 90-

day mortality among critically ill patients with acute kidney injury (AKI). Critically ill adults with acute kidney injury were assigned to continuous renal-replacement therapy in the form of post dilution CVVHDF with an effluent flow of either 40mL per kilogram of body weight per hour (higher intensity) or 25mL per kilogram per hour (lower intensity). The primary outcome measure was death within 90 days after randomisation.

Of the 1508 enrolled patients, 747 were randomly assigned to higher-intensity CRRT and 761 to lower-intensity therapy CRRT. Data on primary outcomes were available for 1464 patients (97.1%): 721 in the higher-intensity group and 743 in the lower-intensity group. The two study groups had similar baseline characteristics and received the study treatment for an average of 6.3 and 5.9 days, respectively (P = 0.35). At 90 days after randomisation, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group (odds ratio, 1.00; 95% confidence interval [CI], 0.81 to 1.23; P = 0.99). At 90 days, 6.8% of survivors in the higher-intensity group (27 of 399), as compared with 4.4% of survivors in the lower-intensity group (18 of 411), were still receiving renal-replacement therapy (odds ratio, 1.59; 95% CI, 0.86 to 2.92; P = 0.14). Hypophosphataemia was more common in the higher-intensity group than in the lower-intensity group (65% vs. 54%, P < 0.001). The conclusion was that in critically ill patients with acute kidney injury, treatment with higher-intensity CRRT did not reduce mortality at 90 days.

Broman *et al*. have conducted two retrospective reviews of Hemosol B0 solution. The first study report is a retrospective study with three groups each containing 14 critically ill AKI patients. With CVVHDF as the modality used for all three groups, the study compared treatment with:

- Group 1: Hemosol B0 solution as both replacement fluid and dialysate;
- Group 2: Phoxilium solution as dialysate and Hemosol B0 solution as replacement fluid; and
- Group 3: Phoxilium solution as both dialysate and replacement fluid.

With respect to acid/base balance, mean pH normalised rapidly in all three groups and, likewise, the mean serum bicarbonate increased consistently during treatment. The mean serum bicarbonate value during treatment in Group 1 (24mmol/L) was normal and the difference in mean sodium bicarbonate values during treatment (Group 1, 24mmol/L; Group 2, 23mmol/L; and Group 3, 22mmol/L) were borderline significantly different (p = 0.045).

The second Broman *et al* study is also a retrospective analysis of the records of 112 patients treated with CVVHDF. Using Hemosol B0 solution exclusively as the replacement fluid, these investigators compared treatment with either the European formulation of Phoxilium solution (N = 76) or Hemosol B0 solution (N = 36) as a dialysate. In this larger population, the mean serum bicarbonate during treatment was in the normal range for both groups and did not significantly differ, although being somewhat higher in the control group compared to the phosphate group. The development of metabolic acidosis as an adverse event (pH < 7.3 and serum bicarbonate < 24mmol/L) was more frequent in the Hemosol B0 solution group (66.7%) than the Phoxilium solution group (55.4%) in this retrospective study. The clinical relevance of this finding cannot be determined due to the different number of patients in the two treatment groups.

5.2 Pharmacokinetic properties

The ready-to-use Hemosol B0 solution must only be administered intravenously. Bioavailability of substitution solutions is 100% as they are administered intravenously.

The distribution of electrolytes and bicarbonate is regulated in accordance with requirements and the metabolic status and residual renal function. The distribution of substitution solutions depends on the osmotic gradient between extra- and intra-cellular space, whereas the distribution of dissolved electrolytes is regulated according to their intra- and extra-cellular concentration gradients. The

active substances of the substitution solution are not metabolised. The elimination of water and electrolytes depends on cellular requirements, metabolic status, residual renal function, and on other routes of fluid losses (e.g., gut, lung, and skin).

No pharmacokinetic interactions between the individual ingredients of Hemosol B0 solution are known.

5.3 Preclinical safety data

Genotoxicity and

There are no specific studies with Hemosol B0 solution for effects on genotoxicity. Given the nature of its components, Hemosol B0 solution is not considered to pose a genotoxic hazard.

Carcinogenicity

There are no specific studies with Hemosol B0 solution for effects on carcinogenicity. Given the nature of its components, Hemosol B0 solution is not considered to pose a carcinogenic hazard.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Small compartment A:	Water for injections
Large compartment B:	Water for injections
	Carbon dioxide.

6.2 Incompatibilities

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

It is the responsibility of the physician to judge the incompatibility of an additive medication with the Hemosol B0 solution 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 medicine, verify it is soluble and stable in water at the pH of Hemosol B0 solution (pH of reconstituted solution is 7.0 to 8.5).

The compatible medication must be added to the reconstituted solution and the solution must be administered immediately.

6.3 Shelf life

18 months as packaged for sale in Polyolefin pack.
The expiry date can be found on the packaging.

After reconstitution

From a chemical point of view, as bicarbonate is present, the reconstituted solution should be used immediately. Other 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

Store between +4°C to +30°C. Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

Hemosol B0 solution is presented in a two-compartment bag made of Polyolefin (polypropylene based, multilayer laminates).

Compartment A is a small compartment of 250mL and Compartment B is a large compartment of 4750mL. The Polyolefin bag includes a peel seal separating the two compartments.

The large compartment B (4750mL) is fitted with two access ports for the connection of the bag with a suitable replacement solution line:

- Access port – 1: an injection port (or spike connector) made of polycarbonate (PC), which is closed with a rubber disc covered by a cap.
- Access port – 2: a luer connector (PC) consisting of a frangible pin (PC) or a valve made of silicone rubber.

The bag is overwrapped with a transparent over pouch made of multilayer copolymers.

Package size: 5000mL.

6.6 Special precautions for disposal and other handling

Disposal

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

Other handling

Use only if the overwrap is not damaged, 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.

Before adding a substance or medication, verify that it is soluble and stable in Hemosol B0, and that the pH range of Hemosol B0 is appropriate (pH of reconstituted solution is 7.0 to 8.5).

The large compartment is fitted with an injection port for the possible addition of other necessary medicines after reconstitution of the solution. Additives may be incompatible. The instructions for use of the medication to be added and other relevant literature must be consulted. After addition, if there is a color change and/or the appearance of precipitates, insoluble complexes, or crystals, do not use.

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.

Use only with appropriate extracorporeal renal replacement equipment.

The electrolyte solution is added to the buffer solution after opening the peel seal and before administration to the patient.

Aseptic technique should be used throughout administration to the patient:

Instructions for use for polyolefin bag with a peel seal separating the two compartments

1. Immediately before use remove the overwrap from the bag and mix the solutions in the two different compartments. Open the seal by holding the small compartment with both hands and squeeze it until an opening is created in the peel seal between the two compartments.
2. Push with both hands on the large compartment until the peel seal between the two compartments is entirely open.

3. 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.
4. The dialysis or replacement line may be connected to either of the two access ports.

Instructions for handling access ports
The Polyolefin bag is supplied with 2 access ports; an *injection* port and a *luer connector* port (the luer connector may be fitted optionally with either a frangible pin or a valve).

1. *The Polyolefin bag fitted with the injection port:* First remove the snap-off cap, then introduce the spike through the rubber septum. Verify that the fluid is flowing freely.
2. *The Polyolefin bag fitted with the luer connector consisting of a frangible pin:* Using aseptic techniques 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 thumb and fingers, break the coloured 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.
3. *The Polyolefin bag fitted with the luer connector consisting of a valve:* 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.
4. 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.
5. The reconstituted solution should be used immediately after removal of the over wrap and after addition of solution A to solution B. If not used immediately, the reconstituted solution should be used within 24 hours including the duration of the treatment.

Any unused product or waste material should be disposed of in accordance with local requirements. The product is for single use in one patient only. Discard any residue immediately after use. Do not use if container is damaged or if solution is not clear.

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

Hemosol B0 solution is distributed in New Zealand by:

Vantive Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060

Phone 0800 436 770

Hemosol B0 solution is distributed in Australia by:

Vantive Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
13 January 2011.

10 DATE OF REVISION OF THE TEXT

26 January 2024.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Amended Sponsor name
8	Amended Sponsor telephone number
8	Removed Sponsor postal address
8	Amended name of distributor in Australia
10	Updated revision date.
References	Updated references
Footer	Updated source document date and Sponsor name

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.