SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

bica*Vera* 1.5% Glucose, 1.75 mmol/l Calcium
Solution for peritoneal dialysis

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

bicaVera 1.5% glucose is delivered in a double chamber bag. One chamber contains the alkaline hydrogen carbonate solution, the other chamber contains the acidic glucose-based electrolyte solution. Mixing of both solutions by opening the median seam between the two chambers results in the ready-to-use solution.

BEFORE RECONSTITUTION

1 litre of acidic glucose based electrolyte solution contains:
active substances:

Sodium chloride	11.57	g
Calcium chloride dihydrate	0.5145	g
Magnesium chloride hexahydrate	0.2033	g
Glucose monohydrate	33.0	g
(equivalent to glucose anhydrous)	30.0	g
Na^+	198.0	mmol/l
Ca^{2+}	3.5	mmol/l
Mg^{2+}	1.0	mmol/l
Chloride	209.0	mmol/l

1 litre of alkaline hydrogen carbonate solution contains:
active substances:

Sodium hydrogen carbonate	5.88	g
Na^+	70	mmol/l
HCO_3^-	70.0	mmol/l

AFTER RECONSTITUTION

1 litre of the ready-to-use solution contains:
active substances:

Sodium chloride	5.786	g
Sodium hydrogen carbonate	2.940	g
Calcium chloride dihydrate	0.2573	g
Magnesium chloride hexahydrate	0.1017	g
Glucose monohydrate	16.5	g
(equivalent to glucose anhydrous)	15.0	g

Na^+	134.0	mmol/l
Ca^{2+}	1.75	mmol/l
Mg^{2+}	0.5	mmol/l
Chloride	104.5	mmol/l
Hydrogen carbonate	34.0	mmol/l
Glucose	83.25	mmol/l

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for peritoneal dialysis
Clear and colourless solution

Theoretical osmolarity: 358 mosm/l
pH ≈ 7.40

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

End-stage (decompensated) chronic renal failure of any origin treated with peritoneal dialysis.

4.2 Posology and Method of Administration

Dosage

bica*Vera* 1.5% glucose is exclusively indicated for the intraperitoneal use.
The mode of therapy, frequency of administration, and dwell time required will be specified by the attending physician.

Continuous ambulatory peritoneal dialysis (CAPD)
Unless otherwise advised, patients will receive an infusion of 2000 ml solution per exchange four times a day. After a dwell time between 2 and 10 hours the solution will be drained.

Adjustment of dosage will be necessary for individual patients.

bica*Vera* 1.5% glucose contains 15 g glucose in 1000 ml solution. According to the dosage instruction up to 30 g glucose are supplied to the body with each bag.

If dilation pain occurs at the commencement of peritoneal dialysis, the solution volume per exchange should be initially reduced to 500 - 1500 ml.

In large patients, and if residual renal function is lost, an increased dose of dialysis will be necessary. In these patients, or patients who tolerate larger volumes, a dose of 2500 ml solution per exchange may be given.

In children the solution volume per exchange should be reduced according to age, size, and body weight (30 – 40 ml/kg body weight).

Automated peritoneal dialysis (APD)

If a machine (sleep safe cycler) is used for intermittent or continous cyclic peritoneal dialysis larger volume bags (3000 ml) providing more than one solution exchange are used. The cycler performs the solution exchanges according to the medical prescription stored in the sleep safe cycler.

Peritoneal dialysis solutions with a high glucose concentration (2.3% or 4.25%) are used when the body weight is above the desired dry weight. The withdrawal of fluid from the body increases in relation to the glucose concentration of the peritoneal dialysis solution. These solutions should be used cautiously to treat the peritoneal membrane with care to prevent dehydration and in order to keep the glucose burden as low as possible.

Peritoneal dialysis is a long-term therapy involving repeated administrations of single solutions.

Method and duration of administration

Patients should proficient at performing peritoneal dialysis before performing it at home. The training should be performed by qualified personnel. The attending physician must ensure that the patient masters the handling techniques sufficiently before the patient performs peritoneal dialysis at home. In case of any problems or uncertainty the attending physician should be contacted.

Dialysis using the prescribed doses should be performed daily.
Peritoneal dialysis should be continued for as long as renal function substitution therapy is required.

Continuous ambulatory peritoneal dialysis (CAPD)

For the step-by-step instruction for use please be referred to paragraph 6.6.
The solution bag is first warmed up to body temperature.
The heating will be performed with a heating plate. The time for heating is about 120 minutes for a 2000 ml bag at a temperature of 22 º C. Details can be read in the instruction manual of the heating plate. A microwave oven must not be used due to the risk of local overheating.

The solutions in the two chambers must be mixed before use. For that purpose roll up the bag from one of the upper ends until the middle seam opens. The solutions in the two chambers are mixed automatically. Then roll up the bag from the upper edge, until the peel seam of the lower triangle is completely opened.

Depending on physician's instructions, the dose should dwell in the peritoneal cavity for 2 to 10 hours (equilibrium time), and then be drained. Depending on the required osmotic pressure, bica*Vera* 1.5% glucose can be used sequentially with other peritoneal dialysis solutions with higher glucose content (i.e. with higher osmolarity).

Automated peritoneal dialysis (APD)

The connectors of the prescribed sleep safe solution bags are inserted in the free sleep safe tray ports and then automatically connected to the sleep safe tubing set by the cycler. The cycler checks the bar codes of the solution bags and gives an alarm when the bags do not comply to the prescription stored in the cycler. After this check the tubing set can be connected to the patient's catheter extension and the treatment be started. The sleep safe solution is automatically warmed up to body temperature by the sleep safe cycler during the inflow into the abdominal cavity. Dwell times and selection of glucose concentrations are carried out according to the medical prescription stored in the cycler (for more details please refer to the operating instructions of the sleep safe cycler).

4.3 Contraindications

For this specific peritoneal dialysis solution

bica*Vera* 1.5% glucose must not be used in patients with severe hypokalemia, severe hypercalcemia.

For peritoneal dialysis in general

Peritoneal dialysis should not be commenced in case of

- recent abdominal surgery or injury, a history of abdominal operations with fibrous adhesions, severe abdominal burns, bowel perforation,
- extensive inflammatory conditions of the abdominal skin (dermatitis),
- inflammatory bowel diseases (Crohn's disease, ulcerative colitis, diverticulitis),
- localized peritonitis,
- internal or external abdominal fistula,
- umbilical, inguinal or other abdominal hernia,
- intra-abdominal tumours,
- ileus
- pulmonary disease (especially pneumonia),
- sepsis,
- extreme hyperlipidemia,
- in rare cases of uremia, which can not be managed by peritoneal dialysis,
- cachexia and severe weight loss, particularly in cases in which the ingestion of adequate protein is not guaranteed,
- patients who are physically or mentally incapable of performing PD as instructed by the physician.

If any of the above mentioned disorders develops during the peritoneal dialysis, the attending physician has to decide on how to proceed.

This peritoneal dialysis solution must not be used for intravenous infusion.

4.4 Special Warnings and Special Precautions for Use

bica*Vera* 1.5% glucose may only be administered after careful benefit-risk assessement in:

- loss of electrolytes due to vomiting and/or diarrhea (a temporary change to a peritoneal dialysis solution containing potassium might then become necessary.)
- hypercalcemia, e.g. due to the administration of calcium-containing phosphate binders: A transient or permanent change to a peritoneal dialysis solution with a lower calcium concentration should be considered.
- digitalis therapy: Regular monitoring of the serum potassium level is mandatory. Severe hypokalemia may necessitate the use of a potassium-containing dialysis solution besides dietary counselling.

The natural metabolic acidosis due to renal failure might not be totally compensated by the 34 mmol/l bicarbonate level of the final solution. Acidosis might be associated with undesirable effects e.g. malnutrition.

A loss of proteins, amino acids, and water-soluble vitamins occurs during peritoneal dialysis. To avoid deficiencies an adequate diet or supplementation should be ensured.

The transport characteristics of the peritoneal membrane may change during long-term peritoneal dialysis primarily indicated by a loss of ultrafiltration. In severe cases peritoneal dialysis must be stopped and hemodialysis commenced.

<u>The monitoring of the following parameters is recommended:</u>

- body weight for the early recognition of over- and dehydration,
- serum sodium, potassium, calcium, magnesium, phosphate, acid base status and blood proteins
- serum creatinine and urea,
- parathormone and other indicators of bone metabolism,
- blood sugar,
- residual renal function in order to adapt the peritoneal dialysis

<u>Elderly patients</u>
The increased incidence of hernia should be considered in elderly patients prior to the start of peritoneal dialysis.

<u>Shelf life of the ready-to-use solution</u>
The ready-to-use solution must be administered within 24 hours after mixing.

<u>Handling</u>
Plastic containers may occasionally be damaged during transport or storage. This can result in a contamination with growth of microorganisms in the dialysis solution. Thus all containers should be carefully inspected for damage prior to connection of the bag and prior to use of the peritoneal dialysis solution. Any damage, even minor,

to connectors, at the closure, container welds and corners must be noted because of possible contamination.

Damaged bags or bags with cloudy content should never be used!

Only use the peritoneal dialysis solution if container and seal are undamaged. In case of doubt the attending physician should decide on the use of the solution.

The overwrap should only be removed before administration.

Do not use before mixing the two solutions.

Aseptic conditions must be maintained during dialysate exchange in order to reduce the risk of infection.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

The use of this peritoneal dialysis solution can lead to a loss of efficacy of other drugs if these are dialysable through the peritoneal membrane. A dose adjustment might be necessary.
A distinct reduction of the serum potassium level can increase the frequency of digitalis-associated adverse reactions. Potassium levels must be monitored particularly closely during concurrent digitalis therapy.

The concomitant administration of calcium-containing drugs as well as vitamin D may cause hypercalcaemia.
The use of diuretic agents may help maintain residual diuresis, but may also result in water and electrolyte imbalances.
In diabetic patients the daily dose of blood sugar reducing medication must be adjusted to the increased glucose load.

4.6 Pregnancy and Lactation

There are no adequate data from use of bica*Vera* solutions in animals studies or in pregnant women.
Caution should be exercised when prescribing to pregnant women or during lactation period.

4.7 Effects on Ability to Drive and Use Machines

When used as prescribed no impairment of the ability to drive and to use machines is known.

4.8 Undesirable Effects

bica*Vera* 1.5% glucose is an electrolyte solution the composition of which is similar to blood.
In addition the physiological buffer bicarbonate is used. In general the solution is tolerated very well.

Possible adverse reactions may result from the peritoneal dialysis itself or may be induced by the peritoneal dialysis solution.

Potential adverse reactions of the peritoneal dialysis solution are
- electrolyte disturbances, e.g hypokalemia, hypercalcaemia in combination with an increased calcium uptake, e.g. by the administration of calcium-containing phosphate binders,
- disturbances in hydration. A rapid decrease in body weight, the drop in blood pressure and/or tachycardia may indicate dehydration; edema, hypertension and possibly dyspnea may indicate overhydration.
- increased blood sugar levels,
- hyperlipidemia
- increase in body weight.

Potential side effects of the treatment mode are
- peritonitis, indicated by cloudy effluent. Later abdominal pain, fever, and malaise (general feeling unwell) may develop or, in very rare cases, generalised blood poisoning (sepsis). The patient should visit the attending physician immediately. The bag with the cloudy effluent should be closed with a sterile cap and brought along for further evaluation.
- skin exit site infection or tunnel infection of the catheter indicated by redness, edema, pain, exudations or crusts. The attending physician should be consulted as soon as possible.
- in- and outflow disturbances of the dialysis solution,
- diarrhea or obstipation,
- dyspnea caused by the elevated diaphragm,
- hernia,
- abdominal dilatation and sensation of fullness,
- shoulder pain.

4.9 Overdose

Any excess of dialysis solution infused in the peritoneal cavity can easily be drained in the drainage bag. In case of too frequent exchanges dehydration and/or electrolyte disturbances might result which necessitate immediate medical attention.

If one or more of the daily exchanges are missed or a too small solution volume has been administered, overhydration and electrolyte disturbances may develop.

Interruption or discontinuation of treatment may result in life-threatening overhydration and uraemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group

Group: Solution for peritoneal dialysis

ATC: B05D B

The electrolyte profile of the solution is basically the same as that of physiological Serum. It has been adapted (e.g. the potassium content) for use in uraemic patients, to enable renal replacement therapy by means of intraperitoneal substance and fluid exchange. Substances which are normally eliminated with the urine, such as urea, creatinine, and water, are removed from the body into the dialysis solution. It should be borne in mind that therapeutic substances may also be eliminated during dialysis, and that a dose adjustment may be necessary.

Individual parameters (patient size and body weight, laboratory parameters, residual renal function, ultrafiltration, required dialysis dose) must be considered to determine the adequate dose and the combination of solutions with differing osmolarity (glucose concentration), and potassium, sodium, and calcium concentrations. The efficacy of therapy should be regularly monitored on the basis of these parameters.

bica*Vera* 1.5% glucose contains bicarbonate - the physiological buffer - instead of lactate or acetate.

5.2 Pharmacokinetic Properties

No animal studies have been performed with the intraperitoneal application of bicarbonate-containing bica*Vera* solutions. Clinical studies in patients on bica*Vera* have shown that dialysate bicarbonate equilibrates with blood bicarbonate within a two-hour dwell time.

5.3 Preclinical Safety Data

Preclinical data revealed no special hazard for humans based on safety pharmacology, single dose toxicity and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hydrochloric acid
Sodium hydroxide
Carbon dioxide
Water for injections

6.2 Incompatibilities

Drugs must be added under aseptic conditions only when medically prescribed. Because of the risk of incompatibility between the dialysis solution and the added drugs only the following drugs may be added up to the mentioned concentration if indicated by the attending physician: heparin 1000 I.U./l, insulin 20 I.U./l, vancomycin 1000 mg/l, teicoplanin 400 mg/l, cefazolin 500 mg/l, ceftazidime 250 mg/l, gentamycin 8 mg/l. After thorough mixing and checking for the absence of any turbidity the peritoneal dialysis solution containing other drugs must be used immediately (no storage).

6.3 Shelf Life

Shelf life within the container: 2 years
Shelf life of the ready-to-use solution prepared as described in section 6.6 and without any additional drugs: 24 hours

6.4 Special Precautions for Storage

Do not store below 4°C.

6.5 Nature and Contents of Container

Double chamber bag:
Bicarbonate solution : glucose-based electrolyte solution = The ratio should be 1:1

Stay safe:
The stay safe system is provided as a double bag system consisting of a non-PVC solution bag made of a multi layer polyolefine foil, containing the gas barrier, a tubing system also made of polyolefines, a system connector (DISC, polypropy-lene), a drainage bag and an outer bag, also made of polyolefine multi layer film.

Sleep safe:
The sleep safe system is provided as a single bag system consisting of a non-PVC solution bag made of a multi layer polyolefine foil, containing the gas barrier, a tubing system, a bag connector both also made of polyolefines and an injection port made of polyolefine/synthetic rubber.

Both stay safe and sleep safe system are wrapped up in a polyolefine/polyester-laminated film.

Pack sizes:

4 bags of 1500 ml
4 bags of 2000 ml
4 bags of 2500 ml
4 bags of 3000 ml
2 bags of 5000 ml

6.6 Instructions for Use and Handling and Disposal

stay safe system:
The solution bag is first warmed to body temperature. This should be done by using an appropriate heater tray. The heating time for a 2000ml bag with a starting temperature of 22°C is approx. 120 min. More detailed information can be obtained from the operating instructions of the bag warmer. The use of microwaves to warm

the solution is not recommended due to the risk of local overheating. After warming the solution you can start with the exchange of the bags.

1. Preparation of the solution
- Place the bag on a solid ground
- Open the overwrap of the bag and seal of the disinfection cap.
- Control the solution bag (label, expiry date, clearness of the solution, integrity of the bag)
- Wash your hands with an antimicrobial washing lotion.
- Roll up the bag from one of the upper ends until the middle seam opens. The solutions in the two chambers are mixed automatically.
- Then roll up the bag from the upper edge, until the peel seam of the lower triangle is completely opened.
- The ready-to-use solution should be used within a maximum of 24 hours after mixing!

2. Preparation of the bag exchange
- Hang the solution bag on the upper hook of the infusion pole, unroll the tubing line of the solution bag, and place the DISC into the organizer. After unrolling the tubing line to the drainage bag, hang the drainage bag on the lower hook of the infusion pole and place the disinfection cap into the organizer.
- Place catheter adapter into the organizer.
- Disinfect your hands and remove the protection cap of the DISC.
- Connect catheter adapter to the DISC.

3. Outflow
- Open the catheter clamp. The outflow starts.
  ⇒Position ●

4. Flush
- Flush the drainage bag with fresh solution (approx. 5 seconds)
  ⇒ Position ●●

5. Inflow
- Connect the solution bag with the catheter.
  ⇒ Position ○◑●

6. Security step
- Close the catheter adapter by putting in the PIN
  ⇒ Position ●●●●

7. Disconnection
- Remove the catheter adapter from the DISC and screw the new disinfection cap to the catheter adapter

8. Closure of the DISC
- Close the DISC with the open end of the protection cap of the used disinfection cap, which is placed in the right hole of the organizer.

9. Check the drained dialysate and dispose of it.

<u>sleep safe system</u>

(for the set up of the sleep safe system please refer to its operating instructions):
Instruction for use of the sleep safe bicaVera system:

1.Preparation of the solution

- Place the bag on a solid ground
- Open the overwrap of the bag and seal of the disinfection cap.
- Control the solution bag (label, expiry date, clearness of the solution, integrity of the bag)
- Wash your hands with an antimicrobial washing lotion.
- Roll up the bag from one of the upper ends until the middle seam opens. The solutions in the two chambers are mixed automatically.
- Then roll up the bag from the upper edge, until the peel seam of the lower triangle is completely opened.
- The ready-to-use solution should be used within a maximum of 24 hours after mixing!

2.Unroll tubing of bag.
3.Remove the protection cap.
4.Insert connector in free sleep safe tray port.
5.The bag is now ready for use with the sleep safe set.

7. MARKETING AUTHORISATION HOLDER

NEPHROMED LTD.
7 Carlebach Street, Tel Aviv, Israel

8. REGISTRATION NUMBER;132 53 31018 00

9. MANUFACTURER:

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