

PHYSIONEAL 40 Glucose 2.27%w/v/22.7 mg/ml Clear-Flex, solution for peritoneal dialysis

1. NAME OF THE MEDICINAL PRODUCT

PHYSIONEAL 40 Glucose 2.27% w/v / 22.7 mg/ml Clear-Flex,
Solution for peritoneal dialysis.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Before mixing

| 1000 ml of electrolyte solution (large chamber "A") contains: | |
|--|---------|
| Active substances: | |
| Glucose monohydrate | 33.3 g |
| equivalent to Glucose anhydrous | 30.3 g |
| Calcium chloride dihydrate | 0.245 g |
| Magnesium chloride hexahydrate | 0.068 g |
| 1000 ml of buffer solution (small chamber "B") contains: | |
| Active substances: | |
| Sodium chloride | 19.95 g |
| Sodium bicarbonate | 9.29 g |
| Sodium (S)-lactate solution | 6.73 g |

After mixing

| 1000 ml of the mixed solution contains: | |
|--|---------|
| Active substances: | |
| Glucose monohydrate | 25.0 g |
| equivalent to Glucose anhydrous | 22.7 g |
| Sodium chloride | 5.38 g |
| Calcium chloride dihydrate | 0.184 g |
| Magnesium chloride hexahydrate | 0.051 g |
| Sodium bicarbonate | 2.10 g |
| Sodium (S)-lactate solution | 1.68 g |

1000 ml of final solution after mixing corresponds to 750 ml of solution A and 250 ml of solution B.

| Composition of the final solution after mixing in mmol/l | |
|--|-------------|
| Glucose anhydrous (C ₆ H ₁₂ O ₆) | 126 mmol/l |
| Na ⁺ | 132 mmol/l |
| Ca ⁺⁺ | 1.25 mmol/l |
| Mg ⁺⁺ | 0.25 mmol/l |
| Cl ⁻ | 95 mmol/l |
| HCO ₃ ⁻ | 25 mmol/l |
| C ₃ H ₅ O ₃ ⁻ | 15 mmol/l |

For the full list of excipients, see section 6.1.

The number '40' in the name specifies the buffer concentration of the solution (15 mmol/l of lactate + 25 mmol/l of bicarbonate = 40 mmol/l).

3. PHARMACEUTICAL FORM

Solution for peritoneal dialysis.
Sterile, clear, colourless solution.

The pH of the final solution is 7.4.
Osmolarity 395 mOsmol/l

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHYSIONEAL 40 is indicated whenever peritoneal dialysis is employed, including:

- Acute and chronic renal failure;
- Severe water retention;
- Severe electrolyte imbalance;
- Drug intoxication with dialysable substances, when a more adequate therapeutic alternative is not available.

PHYSIONEAL 40 bicarbonate/lactate based peritoneal dialysis solutions with a physiological pH are particularly indicated in patients in whom solutions based on lactate buffer only, with a low pH, cause abdominal inflow pain or discomfort.

4.2 Posology and method of administration

Administration

- PHYSIONEAL 40 is intended for intraperitoneal administration only. Not for intravenous administration.
- Peritoneal dialysis solutions may be warmed to 37°C to enhance patient comfort. However, only dry heat (for example, heating pad, warming plate) should be used. Solutions should not be heated in water or in a microwave oven due to the potential for patient injury or discomfort.
- Aseptic technique should be employed throughout the peritoneal dialysis procedure.
- Do not administer if the solution is discolored, cloudy, contains particulate matter or shows evidence of leakage, or if seals are not intact.
- The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis.
- For single use only.
- After removal of the overpouch, immediately open the long-seal (interchamber seal) to mix the two solutions and then open the short SafetyMoon seal (access seal) to allow administration of the mixed solution. The intraperitoneal solution must be infused within 24 hours after mixing.
- For further information on the use of the medicinal product see section 6.6 Instructions for use and handling.

Posology

The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be selected by the physician.

- Adults: patients on continuous ambulatory peritoneal dialysis (CAPD) typically perform 4 cycles per day (24 hours). Patients on automated peritoneal dialysis (APD) typically perform 4-5 cycles at night and up to 2 cycles during the day. The fill volume depends on body size, usually from 2.0 to 2.5 litres.
- Elderly: as for adults.

- Paediatric patients from pre-term newborn infants to adolescents:
Paediatric patients have not been evaluated in clinical studies with PHYSIONEAL 40. Therefore the benefits of PHYSIONEAL 40 have to be balanced versus the risks of side effects in this patient category.
If used in this patient category, the fill volume should be adapted depending on body size (usually 800 to 1400 ml/m² (35-45 ml/kg) per cycle).
However the use of PHYSIONEAL 40 in the **Clear-Flex container** is not recommended in children requiring a fill volume < 1600 ml due to the risk of not detecting a possible misinfusion (administration of the small chamber only). – See section 4.4.

To avoid the risk of severe dehydration, hypovolaemia and to minimise the loss of proteins, it is advisable to select the peritoneal dialysis solution with the lowest osmolarity consistent with fluid removal requirements for each exchange.

4.3 Contraindications

PHYSIONEAL 40 should not be used in patients with:

- uncorrectable mechanical defects that prevent effective PD or increase the risk of infection,
- documented loss of peritoneal function or extensive adhesions that compromise peritoneal function.

4.4 Special warnings and precautions for use

- Peritoneal dialysis should be done with caution in patients with:
 - 1) abdominal conditions, including disruption of the peritoneal membrane and diaphragm by surgery, from congenital anomalies or trauma until healing is complete, abdominal tumors, abdominal wall infection, hernias, fecal fistula, colostomy or ileostomy, frequent episodes of diverticulitis, inflammatory or ischemic bowel disease, large polycystic kidneys, or other conditions that compromise the integrity of the abdominal wall, abdominal surface, or intra-abdominal cavity
 - 2) other conditions including recent aortic graft replacement and severe pulmonary disease.
- Encapsulating Peritoneal Sclerosis (EPS) is considered to be a known, rare complication of peritoneal dialysis therapy. EPS has been reported in patients using peritoneal dialysis solutions including some patients using PHYSIONEAL 40 as part of their PD therapy.
- If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of identification and sensitivity studies of the isolated organism(s) when possible. Prior to identification of the involved organism(s), broadspectrum antibiotics may be indicated.
- Patients with elevated lactate levels should use lactate-containing peritoneal dialysis solutions with caution. It is recommended that patients with conditions known to increase the risk of lactic acidosis [e.g., acute renal failure, inborn errors of metabolism, treatment with drugs such as metformin and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)] must be monitored for occurrence of lactic acidosis before the start of treatment and during treatment with lactate-based peritoneal dialysis solutions.
- When prescribing the solution to be used for an individual patient, consideration should be given to the potential interaction between the dialysis treatment and therapy directed at other existing illnesses. Serum potassium levels should be monitored carefully in patients treated with cardiac glycosides.
- Safety and effectiveness in pediatric patients has not been established.

- In patients with secondary hyperparathyroidism, the benefits and risks of the use of a solution with 1.25 mmol/l calcium, such as PHYSIONEAL 40, should be carefully considered as it might worsen hyperparathyroidism.
- An accurate fluid balance record must be kept and the body weight of the patient must carefully be monitored to avoid over- or underhydration with severe consequences including congestive heart failure, volume depletion and shock.
- In patients with plasma bicarbonate level above 30 mmol/l, the risk of possible metabolic alkalosis should be weighed against the benefits of treatment with this product.
- Protein, amino acids, water soluble vitamins and other medicines may be lost during peritoneal dialysis and may require replacement.
- Overinfusion of PHYSIONEAL 40 solutions into the peritoneal cavity may be characterized by abdominal distension/abdominal pain and/or shortness of breath.
- Treatment of PHYSIONEAL 40 overinfusion is to drain the solution from the peritoneal cavity.
- Excessive use of PHYSIONEAL 40 peritoneal dialysis solution with a higher dextrose (glucose) during a peritoneal dialysis treatment may result in excessive removal of water from the patient.
- Potassium is omitted from PHYSIONEAL 40 solutions due to the risk of hyperkalemia.
 - In situations in which there is a normal serum potassium level or hypokalemia, the addition of potassium chloride (up to a concentration of 4 mEq/l) may be indicated to prevent severe hypokalemia and should be made after careful evaluation of serum and total body potassium, only under the direction of a physician.
- Serum electrolyte concentrations (particularly bicarbonate, potassium, magnesium, calcium and phosphate), blood chemistry (including parathyroid hormone) and haematological parameters should be monitored periodically.
- In patients with diabetes, blood glucose levels should be monitored and the dosage of insulin or other treatment for hyperglycaemia should be adjusted.
- Patients must be instructed to open both the long and the short seals prior to infusion. If only the short SafetyMoon seal opens, infusion of the unmixed solution can cause abdominal pain, hypernatremia and severe metabolic alkalosis. In case of infusion of unmixed solution, the patient should immediately drain the solution and use a newly mixed bag.

4.5 Interaction with other medicinal products and other forms of interaction

- Blood concentration of dialysable medicinal product may be reduced during dialysis. A possible compensation for losses must be taken into consideration.
- Plasma levels of potassium in patients using cardiac glycosides must be carefully monitored as there is a risk of digitalis intoxication. Potassium supplements may be necessary.

4.6 Pregnancy and lactation

There is no clinical experience with PHYSIONEAL 40 during pregnancy and lactation. No data are available from animal studies. The risk-benefit must be assessed. See section 4.4.

4.7 Effects on ability to drive and use machines

End stage renal disease (ESRD) patients undergoing peritoneal dialysis may experience undesirable effects, which could affect the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions (occurring in 1% of patients or more) from the clinical trials and post marketing are listed below.

The most commonly reported Adverse Reaction from the controlled clinical trials with PHYSIONEAL 40 was alkalosis, occurring in approximately 10 % of patients. In most cases, it was based on serum bicarbonate values only and was usually not associated with clinical symptoms.

The adverse drug reactions listed in this section are given following the recommended frequency convention: very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; very rare: $< 0.01\%$, not known (cannot be estimated from available data).

| System Organ Class | Preferred Term | Frequency |
|--|---|--|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | Eosinophilia | Not known |
| METABOLISM AND NUTRITIONAL DISORDERS | Alkalosis Hypokalaemia Fluid retention Hypercalcaemia Hypervolaemia Anorexia Dehydration Hyperglycaemia Lactic Acidosis | Common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon |
| PSYCHIATRIC DISORDERS | Insomnia | Uncommon |
| NERVOUS SYSTEM DISORDERS | Dizziness Headache | Uncommon Uncommon |
| VASCULAR DISORDERS | Hypertension Hypotension | Common Uncommon |
| RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS | Dyspnoea Cough | Uncommon Uncommon |
| GASTROINTESTINAL DISORDERS | Peritonitis Peritoneal membrane failure Abdominal pain Dyspepsia Flatulence Nausea Sclerosing encapsulating peritonitis Cloudy peritoneal effluent | Common Uncommon Uncommon Uncommon Uncommon Uncommon Not known Not known |
| SKIN AND SUBCUTANEOUS DISORDERS | Angioedema Rash | Not known Not known |

| System Organ Class | Preferred Term | Frequency |
|---|---|---|
| MUSCULOSKELETAL, CONNECTIVE TISSUE DISORDERS | Musculoskeletal pain | Not known |
| GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS | Oedema Asthenia Chills Facial oedema Hernia Malaise Thirst Pyrexia | Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Not known |
| INVESTIGATIONS | Weight increased PCO ₂ increased | Common Uncommon |

Other undesirable effects of peritoneal dialysis related to the procedure: bacterial peritonitis, catheter site infection, catheter related complication.

4.9 Overdose

Possible consequences of overdose include hypervolaemia, hypovolaemia, electrolyte disturbances or (in diabetic patients) hyperglycaemia. Refer to section 4.4.

Management of overdose:

Hypervolaemia may be managed by using hypertonic peritoneal dialysis solutions and fluid restriction.

Hypovolaemia may be managed by fluid replacement either orally or intravenously, depending on the degree of dehydration.

Electrolyte disturbances shall be managed according to the specific electrolyte disturbance verified by blood test. The most probable disturbance, hypokalaemia, may be managed by the oral ingestion of potassium or by the addition of potassium chloride in the peritoneal dialysis solution prescribed by the treating physician.

Hyperglycaemia (in diabetic patients) shall be managed by adjusting the insulin dose according to the insulin scheme prescribed by the treating physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Peritoneal Dialytics
ATC code: B05DB

For patients with renal failure, peritoneal dialysis is a procedure for removing toxic substances produced by nitrogen metabolism and normally excreted by the kidneys, and for aiding the regulation of fluid and electrolyte as well as acid base balances.

This procedure is accomplished by administering peritoneal dialysis fluid through a catheter into the peritoneal cavity. Glucose produces a solution hyperosmolar to the plasma, creating an osmotic gradient which facilitates fluid removal from the plasma to the solution. Transfer of substances between the patient's peritoneal capillaries and the dialysis fluid is made across the peritoneal membrane according to the principles of osmosis and diffusion. After dwell time, the

solution is saturated with toxic substances and must be changed. With the exception of lactate, present as a bicarbonate precursor, electrolyte concentrations in the fluid have been formulated in an attempt to normalise plasma electrolyte concentrations. Nitrogenous waste products, present in high concentration in the blood, cross the peritoneal membrane into the dialysis fluid. More than 30% of the patients in the clinical trials were older than 65. The evaluation of the results obtained for this group does not show any difference to the rest of the patients.

In vitro and ex vivo studies have shown evidence of improved biocompatibility indicators of PHYSIONEAL 40 in comparison with standard lactate buffered solution. In addition, clinical studies in limited numbers of patients with abdominal inflow pain have confirmed some symptomatic benefit. To date, however, there are no data available which indicate that clinical complications overall are reduced or that regular use of such solutions might translate into meaningful benefits over the longer-term.

5.2 Pharmacokinetic Properties

Intraperitoneally administered glucose, electrolytes and water are absorbed into the blood and metabolised by the usual pathways.

Glucose is metabolised (1 g of glucose = 4 kilocalories or 17 kilojoules) into CO₂ and H₂O.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid dilute (pH adjuster)
Sodium hydroxide (pH adjuster)
Water for Injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

- Shelf life as packaged for sale:
2 years.
- Shelf life after mixing:
The product, once removed from its overpouch and mixed, should be used within 24 hours.

6.4 Special precautions for storage

Do not store below 4°C.

6.5 Nature and contents of container

The PHYSIONEAL 40 solution is stored inside a two-chamber bag made of a coextruded film (Clear-Flex film) of Polypropylene, Polyamide and a blend of Polypropylene, SEBS and Polyethylene.

On the upper chamber an injection site is welded for drug admixture to the glucose with electrolytes solution. On the lower chamber a valve system is welded for connection to a

suitable administration set allowing dialysis operations.

The lineo connector that may equip the Y transfer line of the twin bag, contains 10.5% of Povidone iodine ointment

The bag is wrapped inside a transparent overpouch made of multilayer copolymers.

Container volumes after reconstitution: 1500 ml (1125 ml of solution A and 375 ml of solution B), 2000 ml (1500 ml of solution A and 500 ml of solution B), 2500 ml (1875 ml of solution A and 625 ml of solution B), 3000 ml (2250 ml of solution A and 750 ml of solution B), 4500 ml (3375 ml of solution A and 1125 ml of solution B), 5000 ml (3750 ml of solution A and 1250 ml of solution B).

The single bag is a two-chamber bag (large chamber "A" and small chamber "B", see section 2) to be used in Automated Peritoneal Dialysis. The twin bag is a two-chamber bag (large chamber "A" and small chamber "B", see section 2) with an integrated disconnect system plus an empty drain bag to be used in Continuous Ambulatory Peritoneal Dialysis

Not all pack sizes may be marketed:

| | | | |
|-------|-----------------|------------------------|---|
| 1.5 l | 5 units per box | two-chamber single bag | Luer connector |
| 1.5 l | 6 units per box | two-chamber single bag | Luer connector |
| 1.5 l | 5 units per box | two-chamber twin bag | Luer connector |
| 1.5 l | 6 units per box | two-chamber twin bag | Luer connector |
| 1.5 l | 5 units per box | two-chamber twin bag | Lineo connector |
| 1.5 l | 6 units per box | two-chamber twin bag | Lineo connector |
| 2.0 l | 4 units per box | two-chamber single bag | Luer connector |
| 2.0 l | 5 units per box | two-chamber single bag | Luer connector |
| 2.0 l | 4 units per box | two-chamber twin bag | Luer connector |
| 2.0 l | 5 units per box | two-chamber twin bag | Luer connector |
| 2.0 l | 4 units per box | two-chamber twin bag | Lineo connector |
| 2.0 l | 5 units per box | two-chamber twin bag | Lineo connector |
| 2.5 l | 3 units per box | two-chamber single bag | Luer connector |
| 2.5 l | 4 units per box | two-chamber single bag | Luer connector |
| 2.5 l | 3 units per box | two-chamber twin bag | Luer connector |
| 2.5 l | 4 units per box | two-chamber twin bag | Luer connector |
| 2.5 l | 3 units per box | two-chamber twin bag | Lineo connector |
| 2.5 l | 4 units per box | two-chamber twin bag | Lineo connector |
| 3.0 l | 3 units per box | two-chamber single bag | Luer connector |
| 3.0 l | 3 units per box | two-chamber twin bag | Luer connector |
| 3.0 l | 3 units per box | two-chamber twin bag | Lineo connector |
| 4.5 l | 2 units per box | two-chamber single bag | Luer connector |
| 5.0 l | 2 units per box | two-chamber single bag | Luer connector |
| 5.0 l | 2 units per box | single two-chamber bag | Luer connector + HomeChoice APD set with Lineo connector |
| 5.0 l | 2 units per box | single two-chamber bag | Luer connector + HomeChoice APD set with Luer connector + clamshell and minicap |

6.6 Special precautions for disposal and other handling

For details on the conditions of administration see section 4.2.

- Detailed instruction on the Peritoneal Dialysis exchange procedure is given to patients by means of training, in a specialised training centre, prior to home use.

- After removal of the overpouch, immediately open the long-seal (interchamber seal) to mix the two solutions and then open the short SafetyMoon seal (access seal) to allow administration of the mixed solution. The intraperitoneal solution must be infused within 24 hours after mixing. Refer to section 4.2.
- Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for: cefazolin (750 mg/l), heparin (2500 IU/L), low molecular weight heparin (Innohep 2500 IU/L), netilmycin (60 mg/l) and vancomycin (1000 mg/l).
- Chemical and physical in-use stability has been demonstrated for 6 hours at 25°C for insulin (Actrapid 4 IU/L, 10 IU/L, 20 IU/L and 40 IU/L).
- Gentamicin (60 mg/l) and tobramycin (60 mg/l) can be added if the solution is used immediately after drug addition.
- Drugs should be added through the medication site in the larger chamber before opening the interchamber peel-seal. Drug compatibility must be checked before admixture and the pH and salts of the solution must be taken into account. The product should be used immediately after any drug addition.
- Discard any unused remaining solution.
- The solution is free from bacterial endotoxins.

7. MARKETING AUTHORISATION HOLDER

To be completed locally

8. MARKETING AUTHORISATION NUMBER

To be completed locally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Last renewal approved in December 2008

10. DATE OF REVISION OF THE TEXT

September 2012