PHYSIONEAL 40 Dextrose 1.5% or 2.5% or 4.25% w/v

1. TRADE NAME OF THE MEDICINAL PRODUCT

PHYSIONEAL 40 Dextrose 1.5% or 2.5% or 4.25% w/v Solution for Peritoneal Dialysis

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PHYSIONEAL 40 Dextrose 1.5% w/v / 15.0 mg/ml, Solution for Peritoneal Dialysis

PHYSIONEAL 40 Dextrose 2.5% w/v / 25.0 mg/ml, Solution for Peritoneal Dialysis

PHYSIONEAL 40 Dextrose 4.25% w/v / 42.5 mg/ml, Solution for Peritoneal Dialysis

The active substances are:

PHYSIONEAL 40 Dextrose

	1.5%	**2.5%**	**4.25%**
Small chamber "A"			
Dextrose monohydrate	41.25 g/l	68.85 g/l	117.14 g/l
Calcium Chloride Dihydrate	0.507 g/l	0.507 g/l	0.507 g/l
Magnesium Chloride Hexahydrate	0.140 g/l	0.140 g/l	0.140 g/l
Large chamber, "B"			
Sodium Chloride	8.43 g/l	8.43 g/l	8.43 g/l
Sodium Bicarbonate	3.29 g/l	3.29 g/l	3.29 g/l
Sodium Lactate	2.63 g/l	2.63 g/l	2.63 g/l
Final solution after mixing			
Dextrose monohydrate	15.0 g/l	25.0 g/l	42.5 g/l
Sodium Chloride	5.38 g/l	5.38 g/l	5.38 g/l
Calcium Chloride Dihydrate	0.184 g/l	0.184 g/l	0.184 g/l
Magnesium Chloride Hexahydrate	0.051 g/l	0.051 g/l	0.051 g/l
Sodium Bicarbonate	2.10 g/l	2.10 g/l	2.10 g/l
Sodium lactate	1.68 g/l	1.68 g/l	1.68 g/l

1000 ml of final solution after mixing corresponds to 362.5 ml of solution A and 637.5 ml of solution B. The pH of the final solution is 7.4.

Composition of the final solution after mixing in mmol/l

Dextrose ($C_6H_{12}0_6H_20$)	75.7 mmol/l	126 mmol/l	214 mmol/l
Sodium (Na+)	132 mmol/l	132 mmol/l	132 mmol/l
Calcium (Ca^{++})	1.25 mmol/l	1.25 mmol/l	1.25 mmol/l
Magnesium (Mg^{++})	0.25 mmol/l	0.25 mmol/l	0.25 mmol/l
Chloride (Cl^-)	95 mmol/l	95 mmol/l	95 mmol/l
Bicarbonate (HCO_3^-)	25 mmol/l	25 mmol/l	25 mmol/l
Lactate ($C_3H_5O_3^-$)	15 mmol/l	15 mmol/l	15 mmol/l
Osmolarity	344 mOsmol/l	395 mOsmol/l	483 mOsmol/l

Other Ingredients:
Water for Injection
PHYSIONEAL 40 is the new name of the medicinal product formerly known as PHYSIONEAL. The number '40' has been added to the name to specify the buffer concentration of the solution (15 mmol/l of lactate + 25 mmol/l of bicarbonate = 40 mmol/l). The composition of the solution remains unchanged.

3. PHARMACEUTICAL FORM

Solution for peritoneal dialysis.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHYSIONEAL 40 is indicated for:

- peritoneal dialysis for the treatment of acute and chronic renal failure with manifestations of severe water retention and severe electrolyte imbalance.
- intoxication with dialyzable substances where adequate alternate treatments are not available.

Bicarbonate/lactate based PHYSIONEAL 40 peritoneal dialysis solutions with a physiological pH are 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

- PHYSIONEAL 40 is intended for intraperitoneal administration only. Not for intravenous administration.
- Peritoneal dialysis solutions may be warmed to 37°C (98.6°F) 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.
- The solution should be warmed in the overpouch to body temperature before use.
- After removal of the overpouch, immediately break the interchamber frangible pin to mix the two solutions. Wait until the upper chamber has completely drained into the lower chamber. Mix gently by pushing with both hands on the lower chamber walls. The intraperitoneal solution must be infused within 24 hours after mixing.
- Aseptic technique should be employed throughout the peritoneal dialysis procedure.
- The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be selected by the physician.
- To avoid the risk of severe dehydration, hypovolemia and to minimise the loss of proteins, it is advisable to select the peritoneal dialysis solution with the lowest level of osmolarity consistent with fluid removal requirements for each exchange. PHYSIONEAL 40 Dextrose 4.25% w/v Solution for Peritoneal Dialysis is a high osmotic pressure fluid and using it for all exchanges may cause dehydration.
- The average frequency is 4 to 5 times a day. The fill volume depends on body size, usually from 2.0 to 2.5 liters.
- So far, there are no data from clinical studies in pediatric patients. In this patient category the benefits of PHYSIONEAL 40 have therefore to be balanced versus the risk of side effects.
- 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.

4.3 Contraindications

PHYSIONEAL 40 is contraindicated for use 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

WARNINGS

- 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 PHYSIONEAL 40.
- 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), broad spectrum antibiotics may be indicated.
- Solutions containing dextrose should be used with caution in patients with a known allergy to corn or corn products. Hypersensitivity reactions such as those due to a corn starch allergy, including anaphylactic/anaphylactoid reactions, may occur. Stop the infusion immediately and drain the solution from the peritoneal cavity if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically 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., severe hypotension or sepsis that can be associated with acute renal failure; inborn errors of metabolism; treatment with drugs such as 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.

PRECAUTIONS

- PHYSIONEAL 40 is intended for intraperitoneal administration only. Not for intravenous administration.
- Do not administer if the solution is discolored, cloudy, contains particulate matter, shows evidence of leakage between chambers or to the exterior, 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.
- An accurate fluid balance record must be kept and the body weight of the patients should carefully be monitored to avoid over- or underhydration with severe consequences including congestive heart failure, volume depletion and shock.
- Protein, amino acids, water soluble vitamins and other medicines may be lost during peritoneal dialysis and may require replacement.
- In renal failure patients, serum electrolyte concentrations (particularly bicarbonate, potassium, calcium, magnesium and phosphate), blood chemistry (including parathyroid hormone and lipid parameters) and hematological parameters should be evaluated periodically.
- In patients with diabetes, blood glucose levels should be monitored during and following dialysis with dextrose-containing solutions and the dosage of insulin or other treatments for hyperglycemia should be adjusted.
- In patients with secondary hyperparathyroidism, the benefits and risks of the use of dialysis solution with a low calcium content such as PHYSIONEAL 40 should be carefully considered as it might worsen hyperparathyroidism.
- Safety and effectiveness in pediatric patients has not been established. Therefore use is not recommended in children (less than 18 years).
- In patients with plasma bicarbonate level above 30 mmol/l, the risk of possible metabolic alkalosis should be weighed against the benefit of treatment with this product. Serum bicarbonate levels should be monitored regularly.
- 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 or 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; and advanced pregnancy and
  2) other conditions including aortic graft placement and severe pulmonary disease, malnutrition or severe disorders of lipid metabolism. In the individual case, the benefits for the patient must be weighed against the possible complications.
- 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.

- Improper clamping or priming sequence may result in infusion of air into the peritoneal cavity, which may result in abdominal pain and/or peritonitis.
- In case of infusion of unmixed solution, the patient should immediately drain the solution and use a newly mixed bag.

4.5 Interactions with other medicinal products and other forms of interaction
No interaction studies have been conducted with PHYSIONEAL 40. Blood concentration of other dialyzable medicinal products may be reduced during dialysis.

4.6 Pregnancy and lactation
There is no clinical experience with PHYSIONEAL 40 during pregnancy and lactation. No data are available from animal studies. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing PHYSIONEAL 40.

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 Adverse Reactions
The adverse reactions within this section represent those adverse reactions that are thought to have an association with the use of PHYSIONEAL 40 or in conjunction with performing the peritoneal dialysis procedure.

4.8.1 Adverse Reactions from Clinical Trials
In clinical trials with PHYSIONEAL 40 alkalosis occurred in approximately 10% of patients.

Frequency[a] of COMMON Adverse Reactions

System Organ Class	Preferred Term	Percentage of Patients
METABOLISM AND NUTRITIONAL DISORDERS	Alkalosis[b]	3.7
	Hypokalemia	1.3
	Fluid retention	1.0
	Hypercalcemia	1.0
VASCULAR DISORDERS	Hypertension	2.3
GASTROINTESTINAL DISORDERS	Peritonitis	1.3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus	1.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema	2.3
	Asthenia	1.0
INVESTIGATIONS	Weight increased	1.3

Frequency[a] of UNCOMMON adverse reactions

System Organ Class	Preferred Term	Percentage of Patients
NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL	Benign neoplasm of skin	0.3

Frequency[a] of UNCOMMON adverse reactions		
System Organ Class	**Preferred Term**	**Percentage of Patients**
CYSTS AND POLYPS)		
METABOLISM AND NUTRITIONAL DISORDERS	**Hypervolemia**	0.7
	Anorexia	0.3
	Dehydration	0.3
	Hyperglycemia	0.3
	Hyperphosphatemia	0.3
	Lactic acidosis	0.3
PSYCHIATRIC DISORDERS	**Insomnia**	0.3
NERVOUS SYSTEM DISORDERS	**Dizziness**	0.7
	Headache	0.3
	Hypertonia	0.3
CARDIAC DISORDERS	**Arrhythmia**	0.3
	Cardiomegaly	0.3
VASCULAR DISORDERS	**Hypotension**	0.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**Dyspnea**	0.7
	Cough	0.3
	Respiratory acidosis	0.3
GASTROINTESTINAL DISORDERS	**Peritoneal membrane failure[c]**	0.7
	Abdominal pain	0.7
	Dyspepsia	0.7
	Flatulence	0.7
	Nausea	0.7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**Chills**	0.7
	Facial edema	0.7
	Hernia	0.3
	Malaise	0.3
	Thirst	0.3
INJURY POISONING AND PROCEDURAL COMPLICATIONS	**Procedural complication**	0.3
INVESTIGATIONS	**Blood lactate**	0.7

Frequency[a] of UNCOMMON adverse reactions		
System Organ Class	**Preferred Term**	**Percentage of Patients**
	dehydrogenase increased	
	Laboratory test abnormal	0.7
	PCO_2 increased	0.7
	Alanine aminotransferase increased	0.3
	C reactive protein increased	0.3
	Creatinine renal clearance decreased	0.3
	Gammaglutamyl transferase increased	0.3

a) Frequency has been evaluated using the following criteria: 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).
b) Reported in PHYSIONEAL 40 only (N=4/46)

c) MedDRA LLT (lower level term) = lack of ultrafiltration; PT (preferred term) = peritoneal membrane failure; HLT (high level term) = peritoneal and retroperitoneal disorders; HLGT (high level group term) = peritoneal and retroperitoneal conditions; SOC (System Organ Class) =gastrointestinal disorders.

4.8.2 Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These reactions are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

INFECTIONS AND INFESTATIONS: Peritonitis bacterial, Catheter site infection

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Eosinophilia

GASTROINTESTINAL DISORDERS: Encapsulating peritoneal sclerosis, Peritoneal cloudy effluent, Abdominal discomfort

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema, Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Musculoskeletal pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Catheter related complication, Pyrexia

Undesirable effects of peritoneal dialysis include procedure and solution related problems.

Those which are related to the procedure include abdominal pain, bleeding, peritonitis (which is followed by abdominal pain, cloudy effluent and sometimes fever), infection around the catheter (signs of inflammation: redness and secretion), catheter blockage, ileus shoulder pain, hernia of the abdominal cavity.

Those which are generally related to peritoneal dialysis solutions are seen less frequently than those related to the procedure and include weakness, fainting, tiredness, muscle cramping, headache, respiratory symptoms associated with pulmonary oedema and electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia).

4.9 Overdose

There is a potential for overdose resulting in hypervolemia, hypovolemia, electrolyte disturbance or hyperglycaemia. Excessive use of PHYSIONEAL 40 peritoneal dialysis solution with 4.25% Dextrose during a peritoneal dialysis treatment can result in significant removal of water from the patient.

Management of Overdose:

- Hypervolemia may be managed by using hypertonic peritoneal dialysis solutions and fluid restriction. Hypovolemia may be managed by fluid replacement either orally or intravenously, depending on the degree of dehydration.
- Electrolyte disturbances may be managed according to the specific electrolyte disturbance verified by blood testing. The most probable disturbance, hypokalemia 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.
- Hyperglycemia in diabetic patients may be managed by adjusting the insulin dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Solutions for Peritoneal Dialysis (code ATC: B 05DB.

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. 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 arid 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. Dextrose produces a solution hyperosmolar to the plasma, creating an osmotic gradient which facilitates fluid removal from the plasma to the solution.

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 dextrose, buffer, electrolytes and water are absorbed into the blood and metabolised by the usual pathways.

Dextrose is metabolised (1 g of dextrose = 4 kilocalories or 17 kilojoules) into CO_2 and H_2O, provided all calories are spent as energy. Excess calories will be stored as fat.

5.3 Preclinical safety data

Complete preclinical evaluation of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity and carcinogenicity of PHYSIONEAL 40 has not been performed and is partly not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

Incompatibilities have to be checked before admixture. The product should be used immediately after any drug addition. Compatibility has been demonstrated with insulin.

Aminoglycosides should not be mixed with penicillins due to chemical incompatibility.

Consult with pharmacist familiar with peritoneal dialysis, if available. If, in the informed judgment of the physician, it is deemed advisable to introduce additives, use aseptic technique.

Shelf-life after reconstitution. The product, once removed from its overpouch and mixed, should be used within 24 hours.

Refer also to the section 6.5. Instructions for use and handling

6.3 Special precautions for storage
No special precautions for storage. Do not freeze.

6.4 Nature and contents of container
The PHYSIONEAL 40 solution is hermetically sealed inside a two-chambered bag manufactured from medical grade plasticised PVC.

The upper chamber is fitted with an injection port for drug admixture to the glucose with electrolytes solution. The lower chamber is fitted with a port for connection to a suitable administration set allowing dialysis operations.

The bag is sealed inside a transparent overpouch obtained by thermic fusion and made of multilayer copolymers.

Container volumes after reconstitution: 2000 ml (725 ml of solution A and 1275 ml of solution B), 2500 ml (906 ml of solution A and 1594 ml of solution B).

Pack sizes:
The single bag is a two-chamber bag (small chamber “A” and large chamber “B”, see section 2). The twin bag is a two chamber bag (small chamber "A" and large chamber “B”, see section 2) plus a drain bag.

PHYSIONEAL 40 is available in the following pack sizes:

2. 0 l	5 units per box	single two-chamber bag	Luer connector
2. 0 l	5 units per box	twin two-chamber bag	Luer connector
2.5 l	4 units per box	single two-chamber bag	Luer connector
2.5 l	4 units per box	twin two-chamber bag	Luer connector

*Not all presentations are available.

6.5 Instructions for use and handling
- Detailed instruction on the CAPD exchange procedure is given to patients by means of training, in a specialised training centre, prior to home use.
- In the case of damage, the container should be discarded.
- Drugs should be added through the medication port in the glucose chamber before breaking the interchamber frangible pin. The product should be used immediately after any drug addition.
- After removal of the overpouch, immediately break the interchamber frangible pin to mix the two solutions. Wait until the glucose chamber has completely drained into the buffer chamber. Mix gently by pushing with both hands on the buffer chamber walls. The solution should be infused within 24 hours after mixing.
- The pH and salts of the solution must be taken into account for compatibility before adding to the solutions.
- Discard any unused remaining solution.
- For single use only.

NAME AND ADDRESS OF MANUFACTURER
Baxter Healthcare SA, Singapore Branch

2 Woodlands Industrial Park D Street 2, Singapore 737778

MARKETING AUTHORIZATION HOLDER
Baxter Healthcare (Thailand) Co. Ltd
Bangkok, Thailand

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