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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Physioneal 40 Glucose 1.36% w/v / 13.6 mg/ml
Physioneal 40 Glucose 2.27% w/v / 22.7 mg/ml
Physioneal 40 Glucose 3.86% w/v / 38.6 mg/ml
Solutions for peritoneal dialysis

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Physioneal 40 Glucose 1.36% w/v / 13.6 mg/ml

Before mixing

1000 ml of electrolyte solution (Small chamber "A")	
Active substances:	
Glucose Monohydrate	41.25 g
equivalent to Anhydrous Glucose	37.5 g
Calcium Chloride Dihydrate	0.507 g
Magnesium Chloride Hexahydrate	0.140 g
1000 ml of buffer solution (Large chamber "B")	
Active substances:	
Sodium Chloride	8.43 g
Sodium Bicarbonate	3.29 g
Sodium (S)-Lactate	2.63 g

After mixing

1000 ml of the mixed solution contains:	
Active substances:	
Glucose monohydrate	15.0 g
equivalent to Anhydrous Glucose	13.6 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	1.68 g

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	
Glucose anhydrous (C ₆ H ₁₂ O ₆)	75.5 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
Osmolarity	344 mOsmol/l

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Physioneal 40 Glucose 2.27% w/v / 22.7 mg/ml

Before mixing

1000 ml of electrolyte solution (Small chamber "A")	
Active substances:	
Glucose Monohydrate	68.85 g
equivalent to Anhydrous Glucose	62.6 g
Calcium Chloride Dihydrate	0.507 g
Magnesium Chloride Hexahydrate	0.140 g
1000 ml of buffer solution (Large chamber "B")	
Active substances:	
Sodium Chloride	8.43 g
Sodium Bicarbonate	3.29 g
Sodium (S)-Lactate	2.63 g

After mixing

1000 ml of the mixed solution contains:	
Active substances:	
Glucose monohydrate	25.0 g
equivalent to Anhydrous Glucose	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	1.68 g

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	
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
Osmolarity	395 mOsmol/l

Physioneal 40 Glucose 3.86% w/v / 38.6 mg/ml

Before mixing

1000 ml of electrolyte solution (Small chamber "A")	
Active substances:	
Glucose Monohydrate	117.14 g
equivalent to Anhydrous Glucose	106.5 g
Calcium Chloride Dihydrate	0.507 g
Magnesium Chloride Hexahydrate	0.140 g
1000 ml of buffer solution (Large chamber "B")	
Active substances:	
Sodium Chloride	8.43 g
Sodium Bicarbonate	3.29 g
Sodium (S)-Lactate	2.63 g

After mixing

1000 ml of the mixed solution contains:	
Active substances:	
Glucose monohydrate	42.5 g
equivalent to Anhydrous Glucose	38.6 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	1.68 g

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	
Glucose Anhydrous (C ₆ H ₁₂ O ₆)	214 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
Osmolarity	483 mOsmol/l

For excipients see 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.

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

- For intraperitoneal administration only.
- The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be selected by the physician.
- Adults: an average of 4 to 8 peritoneal dialysis exchanges per day. The fill volume depends on body size, usually from 2.0 to 2.5 litres.
- Elderly: as for adults.
- 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.
- 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 900-1100 ml/m² (35-45 ml/kg) per exchange).
- 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.
- 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.
- For further information on the use of the medicinal product see section 6.6 Instructions for use and handling.

4.3 Contra-indications

There are no absolute contra-indications to peritoneal dialysis, several conditions warrant special precautions, see section 4.4. Special warnings and precautions for use.

4.4 Special warnings and special precautions for use

- The solution for peritoneal dialysis must not be used for intravenous infusion.
- It is generally not advisable to use peritoneal dialysis in the presence of:
 - o serious conditions affecting the abdominal wall (e.g. skin infections or burns, recent surgery, hernia)
 - o serious conditions affecting the abdominal cavity (e.g. ascites, ileus, adhesions, bowel perforation, diaphragmatic defects, tumours and advanced pregnancy – see section 4.6)
 - o severe respiratory insufficiency,
 - o malnutrition or severe disorders of lipid metabolism.
 In the individual case, the benefits of the patient must be weighed against the possible complications.

- 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.
- 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 and phosphate), blood chemistry (including parathyroid hormone) and haematological parameters should be evaluated periodically.
- In patients with diabetes, blood glucose levels should be monitored and the dosage of insulin or other treatment for hyperglycaemia should be adjusted.
- 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.

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 glucosides 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

Physioneal 40 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

The most commonly reported Adverse Reaction from the controlled clinical trials 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.

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

	ADR	Frequency	Procedure related	Solution related
Metabolic and Nutritional	Alkalosis	Common	Yes	Yes
	Hyperglycaemia	Common	Yes	Yes
	Hypercalcaemia	Common	Yes	
	Hypokalaemia	Common	Yes	Yes
	Decreased Ultrafiltration	Common	Yes	
	pCO ₂ increased	Uncommon	Yes	Yes
	Lactic Acidosis	Uncommon	Yes	Yes
	Hypervolaemia	Uncommon	Yes	
CardioVascular System	Hypertension	Common	Yes	
Body General	Abdominal pain	Common	Yes	
	Asthenia	Uncommon	Yes	
	Chills	Uncommon	Yes	
	Headache	Uncommon	Yes	
	Peritonitis	Uncommon	Yes	
Nervous system	Dizziness	Uncommon	Yes	

Frequencies are defined as:

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

All of the above reactions are also seen with conventional lactate-containing peritoneal dialysis solutions and are reported in the literature.

Other undesirable effects of peritoneal dialysis related to the procedure or to the solution are often reported in the literature.

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

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

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.

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

Water for Injections.

6.2 Incompatibilities

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

6.3 Stability 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 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: 1500 ml (544 ml of solution A and 956 ml of solution B), 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).

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

6.6 Instructions for use and handling

- 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.
- The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be selected by the physician.
- In the case of damage, the container should be discarded.
- The solution for peritoneal dialysis must not be used for intravenous infusion.
- Do not administer unless solution is clear.
- Aseptic technique should be observed throughout the bag change procedure.
- 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.
- The solution should be warmed to body temperature before use, in order to decrease discomfort on infusion and heat loss. This should be done using dry heat, using a warming plate specially designed for this purpose. The bag should not be immersed in water to warm it. Microwave oven must not be used to warm the solution.
- Drugs should be added through the medication port in the top chamber before breaking the interchamber frangible pin. 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.
- For single use only.
- The solution is free from bacterial endotoxins.

7. DRUG REGISTRATION NO.:

Physioneal 40 Glucose 1.36 % w/v: 126333048900

Physioneal 40 Glucose 2.27 % w/v: 126343049000

Physioneal 40 Glucose 3.86 % w/v: 126353049100

8. MANUFACTURER

Baxter Healthcare S.A. Ireland.

9. IMPORTER

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