PHYSIONEAL 40 GLUCOSE SOLUTION FOR PERITONEAL DIALYSIS

Name of the Medicine: Physioneal 40 Glucose (%) Solution for peritoneal dialysis

Physioneal 40 Glucose 1.36% w/v / 13.6 mg/mL Solution for Peritoneal Dialysis
Physioneal 40 Glucose 2.27% w/v / 22.7 mg/mL Solution for Peritoneal Dialysis
Physioneal 40 Glucose 3.86% w/v / 38.6 mg/mL Solution for Peritoneal Dialysis

Composition:

Composition of the solution in each compartment before mixing in g/L			
	Glucose 1.36%	**Glucose 2.27%**	**Glucose 3.86%**
Small Bag "A"			
Anhydrous Glucose	37.50	62.60	106.50
Calcium Chloride (Dihydrate)	0.507	0.507	0.507
Magnesium Chloride (Hexahydrate)	0.140	0.140	0.140
Large Bag "B"			
Sodium Chloride	8.43	8.43	8.43
Sodium Bicarbonate	3.29	3.29	3.29
Sodium Lactate	2.63	2.63	2.63
Final Solution After Mixing			
Anhydrous Glucose	13.6	22.7	38.6
Sodium Chloride	5.38	5.38	5.38
Calcium Chloride (Dihydrate)	0.184	0.184	0.184
Magnesium Chloride (Hexahydrate)	0.051	0.051	0.051
Sodium Bicarbonate	2.10	2.10	2.10
Sodium Lactate	1.68	1.68	1.68

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 1.36%	**Glucose 2.27%**	**Glucose 3.86%**
Anhydrous glucose ($C_6H_{12}O_6$)	75.5	126	214
Sodium (Na+)	132	132	132
Calcium (Ca^{++})	1.25	1.25	1.25
Magnesium (Mg^{++})	0.25	0.25	0.25
Chloride (Cl^-)	95	95	95
Bicarbonate (HCO_3^-)	25	25	25
Lactate ($C_3H_5O_3^-$)	15	15	15
Osmolarity*	344 mOsmol/L	395 mOsmol/L	483 mOsmol/L

*Osmolarity is equivalent to osmolality in infinitively diluted conditions, including total dissociation of ingredients.

Description:

Physioneal 40 is a sterile, clear, colourless solution.

Pharmacology:

Pharmacodynamic properties –

For use in patients with renal failure to aid the regulation of fluid and electrolytes 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 and diffusion. After dwell time, the solution is saturated with metabolic 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. Glucose produces a solution hyperosmolar to the plasma, creating an osmotic gradient which facilitates fluid removal from the plasma to the solution.

Pharmacokinetic properties –

Intraperitoneally administered glucose, buffer, 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 CO_2 and H_2O.

Clinical Trials:

To date a total of 226 patients have been exposed to Physioneal 40 in a total of 6 controlled clinical trials. The exposure time ranged from single dwells (18 patients) to up to one year’s exposure (70 patients in 6 month study, 43 continued for full year). No pregnant or lactating women or children were studied and there is no long-term survival data.

Most of the trials were designed to demonstrate equivalence with the control product. In all studies there were no significant changes in the residual renal function (RRF), weekly

Kt/V and normalised creatinine clearances when patients switched from Dianeal PD4 to Physioneal 40, and no statistically significant differences between the control (Dianeal PD4) arms of these studies and the Physioneal 40 arms. Ultrafiltration is maintained when the buffer is changed from pure lactate to a bicarbonate/lactate combination. There was no difference between Physioneal 40 and Dianeal PD4 with regard to maintenance of calcium and magnesium homeostasis. Acid-base homeostasis was assessed from measurement of the plasma bicarbonate. In all studies the change from baseline (or between group differences) was always within the pre-defined equivalence targets. Physioneal thus corrects acidosis as well as Dianeal.

There did not seem to be any obvious trends across the various Physioneal 40 trials regarding deaths or withdrawals due to adverse events.

PIVOTAL STUDIES

REP-RENAL-REG-029

Study design

Randomised, open-label, comparative study to assess the bioequivalence of a bicarbonate based peritoneal dialysis [bicarb/lactate 25/15mmol/L] solution compared to lactate (40mmol/L) buffer solution.

Primary Variable

Plasma bicarbonate levels.

The two preparations were considered equivalent if the 90% confidence intervals for the treatment difference fell entirely within ± 3.0mmol/L

Results

Base line demographics and plasma bicarbonate levels for subjects in study REP-RENAL-REG-029

REP-RENAL-REG-029	ITT population	
	Control	Physioneal
Total No. Randomised	36	70
Mean Age (yrs) **Range**	56.6 23 – 76	55.1 26 – 77
Gender % Males	50	60
Previous peritonitis (% subjects)	14.3	18.9
Duration of dialysis at baseline (yrs)	1.6	1.8
Duration of CADP at baseline (yrs)	1.3	1.5
Bicarbonate at baseline mmol/L (SD)	26.3 (3.4)	26.4 (3.0)
Bicarbonate at 3 months (SD)	27.3 (3.0)	28.0 (2.9)
Treatment difference	**0.79** (90% CI 0.26, 1.31)	
Bicarbonate at 6 months (SD)	27.2 (3.1)	27.9(2.9)
Treatment difference	**0.78** (90% CI 0.31, 1.26)	

After three to six months there were small statistically significant treatment differences in plasma bicarbonate levels. 90% of confidence intervals for the treatment differences were within ±3mmol/L of bicarbonate and the treatments are considered to be equivalent. There were no statistically significant correlations between bicarbonate levels and age or normalised Residual Renal Function at 6 months for either treatment, but there was a significant negative correlation between calcium carbonate dose and bicarbonate levels in the Physioneal group.

Subjects treated with Physioneal recorded significantly more alkalosis events than those treated with the lactate (40mmol/L) buffer solution.

REP-RENAL-REG-030-A

Study design

Study designed to subjectively evaluate inflow pain during CAPD with a 28mM bicarbonate solution, Physioneal and Dianeal in 18 subjects who had previously experienced pain during dialysis treatment. This was a single-blind, randomised crossover study where pain was assessed during two single infusions of each solution over a one to three week period, with each participant receiving six single infusions in random order. Test solutions were: bicarbonate 38mM (pH 7.0-7.4); Bicarbonate lactate 25/15 mM (pH 7.0 – 7.4) and Dianeal PD4 (40mM lactate) (pH 5.0 – 5.2). All three solutions contained 3.86% glucose in a two-litre bag.

Primary Variable

The primary endpoint variable was pain during the infusion and subjects were evaluated over a three hour period that included the dwell and drain times of the solution. Pain severity was measured on a five-point visual analogue scale (none, mild, moderate, severe and very severe). The McGill Pain Questionnaire (MPQ) was used to assess the pain severity / intensity and provide verbal descriptors of pain.

Results

Baseline demographics and subjective pain scores (range 0 – 5) for subjects in study REP-RENAL-REG-030A

REP-RENAL-REG-030 A	**ITT population**			
Total No. Randomised	18			
Mean Age (yrs)	53.5			
Range	27 - 75			
Gender % Males	56			
Previous peritonitis in last 6 months (% subjects)	50			
Duration of dialysis at baseline (mean yrs)	2.0			
	Evaluable population			
	Dianeal	**Bicarb.**	**Physioneal**	**P value**
Total No. of infusions	34	34	34	
Peak pain score during infusion (Range)	1.50 (0-3)	0.59 (0-3)	0.44 (0-2)	0.0001
Treatment difference	**Physioneal vs Dianeal PD4**			**0.001**
Peak pain score during dwell (Range)	0.44 (0-3)	0.47 (0-3)	0.21 (0-2)	0.083
Treatment difference	**Physioneal vs Dianeal PD4**			**0.001**
Peak pain score during drain (Range)	0.15 (0-1)	0.32 (0-3)	0.06 (0-2)	0.035
Treatment difference	**Physioneal vs Dianeal PD4**			**0.325**

There was a statistically significant treatment difference in peak pain scores during the infusions (P=0.0001). Physioneal solution produced lower pain scores than Dianeal. However, this difference has not been confirmed from larger studies. Numerous variables could affect pain related to the dialysis procedure (including ones related to the dialysis solution, such as catheter placement, that can affect the validity of clinical trials).

Indications:

Physioneal 40 is indicated for use in peritoneal dialysis in patients with acute or chronic renal failure.

Contraindications:

There are no known contra-indications to peritoneal dialysis; several conditions warrant special precautions, see Precautions section.

Precautions:

- Encapsulating Peritoneal Sclerosis (EPS) is considered to be known, rare complication of peritoneal dialysis therapy. EPS has been reported in patients using peritoneal dialysis solutions including PHYSIONEAL.
- If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of identification of the involved organism(s) where possible. Prior to identification of the involved organism(s), broard-spectrum antibiotics may be indicated.
- 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 with cardiac glycosides.
- Azotemic diabetics require careful monitoring of insulin requirements during and following dialysis with glucose-containing solutions.
- 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, faecal fistula or colostomy, large polycystic kidneys, or other conditions that comprise the integrity of the abdominal wall, abdominal surface, or intra-abdominal cavity; 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.
- Physioneal is intended for intraperitoneal administration only. Not for intravenous administration.
- Do not administer if the solution is discoloured, cloudy, contains particulate matter or shows evidence of leakage or if seals are intact.
- The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis.
- Safety and effectiveness in paediatric patients have not been established.
- An accurate fluid balance record must be kept and the body weight of the patient should carefully be monitored to avoid over- or under hydration 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, magnesium, 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 secondary hyperparathyroidism, the benefits and risks of the use of dialysis solution with low calcium content such as Physioneal 40 should be carefully considered as it might worsen hyperparathyroidism.
- 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. Serum bicarbonate levels should be monitored regularly.
- Overinfusion of PHYSIONEAL solutions into the peritoneal cavity may be characterised by abdominal distension/abdominal pain and/or shortness of breath.
- Treatment of PHYSIONEAL overinfusion is to drain the solution from the peritoneal cavity.
- Excessive use of PHYSIONEAL peritoneal dialysis solution with a higher glucose during peritoneal dialysis treatment may result in excessive removal of water from the patient.
- Potassium is omitted from PHYSIONEAL solutions due to the risk of hyperkalemia.
    - In situations in which there is normal serum potassium level 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.

Carcinogenicity, mutagenicity and impairment of fertility -

Long-term carcinogenicity studies of Physioneal 40 have not been done. Physioneal 40 was not mutagenic in bacterial gene mutation assays. Potential effects on male and female fertility are unknown.

Use in pregnancy (Category B2) –

The potential effects of Physioneal 40 on reproduction have not been adequately studied in animals. There is insufficient experience with the use of dialysis fluids in pregnant women.

Women of childbearing potential should be treated with Physioneal 40 only when adequate contraceptive precautions have been taken. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Physioneal.

Use in lactation -

There are no available data from animal studies on the effects of Physioneal 40 administered during lactation. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Physioneal.

Interactions with other medicines-–

No interaction studies have been conducted with PHYSIONEAL.
Blood concentration of dialyzable drugs 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.

Adverse reactions:

The main adverse events reported for pivotal study REP-RENAL-REG-029 were alkalosis, acidosis and peritonitis. These adverse events were reported by 97.2% and 95.7% of subjects in the control and physiological treatment groups respectively. Subjects treated with Physioneal 40 recorded significantly more alkalosis events than those treated with Dianeal. For pivotal study REP-RENAL-REG-30A, the main adverse events reported were pruritus and sweating.

In clinical trials with PHYSIONEAL 40 the following adverse reactions have been noted: benign neoplasm of the skin, alkalosis, fluid retention, hypercalcaemia, hypervolaemia, anorexia, dehydration, hyperphosphatemia, lactic acidosis, insomnia, dizziness, hypertonia, arrhythmia, cardiomegaly, hypertension, hypotension, dyspenea, cough, respiratory acidosis, peritoneal membrane failure, dyspepsia, flatulence, nausea, pruritis, asthenia, chills, facial oedema, malaise, thirst, procedural complication, weight increase, blood lactate dehydrogenase increased, laboratory test abnormal PCO_2 increased, alanine aminotransferase increased C reactive protein increased, creatinine renal clearance decreased, and gamma glutamyltransferase increased.

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, and 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. hypokalemia, hypocalcaemia).

Post marketing experience from August 1998 until September 2001 indicate that, with the exception of data from 1999, adjusted peritonitis incidence rates submitted to the European Dialysis Solutions Registry were similar for both Physioneal 40 and Dianeal solutions.

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 DISORDER: Eonsinophilia

GASTROINTESTINAL DISORDERS: Sclerosing encapsulating peritonitis, Peritoneal cloudy effluent, Abdominal discomfort

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Musculoskeletal pain

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

Dosage and administration:

Dosage -

Intraperitoneal administration only. Not for intravenous administration.

- *Adult***:**
    - 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.

- Patients on continuous ambulatory peritioneal dialysis (CADP) 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.

- *Children:*

  To date, there are no data from clinical studies in paediatric patients.

- *Elderly:*

  The evaluation of the results obtained for this group does not show any difference to the rest of the patients.

Preparation for administration-

- The solution should be warmed to 37^0C in the overpouch to enhance patient comfort. However, only dry heat (eg heating pad, warming plate) should be used. Solutions should not be heated in water or in a microwave oven.
- Aseptic technique should be employed throughout the peritoneal dialysis procedure.
- Do not administer if the solution is discoloured, 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.
- Discard any unused remaining solution.
- For single use only.
- 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 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 pH and salts of the solution must be taken into account for compatibility before adding to the solution.

Overdosage:

Possible consequences of overdose include hypervolemia, hypovolemia, electrolyte disturbances or (in diabetic patients) hyperglycaemia. Excessive use of PHYSIONEAL peritoneal dialysis solution with 3.68% glucose during a peritoneal dialysis treatment can result in significant removal of water from the patient.

Presentation:

Container -

The Physioneal 40 solution is hermetically sealed inside a two-chamber 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) and 2500 mL (906 mL of solution A and 1594 mL of solution B).

Physioneal 40 is available in 3 strengths:

Physioneal 40 Glucose 1.36% w/v / 13.6 mg/mL Solution for Peritoneal Dialysis
Physioneal 40 Glucose 2.27% w/v / 22.7 mg/mL Solution for Peritoneal Dialysis
Physioneal 40 Glucose 3.86% w/v / 38.6 mg/mL Solution for Peritoneal Dialysis

Physioneal 40 is available in 2 presentations:

- Single bag: Two-chamber bag in 1500mL, 2000mL, 2500mL.
- Twin bag: Two-chamber bag in 1500mL, 2000mL, 2500mL. A drainage bag is attached.

Shelf life and Storage Conditions

Shelf life

The shelf life of the product in the overpouch is 2 years.

Shelf life after reconstitution

The product, once removed from its overpouch and mixed, should be used within 24 hours.

Storage conditions –

Store below 30° C. Do not freeze.

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 case of damage the container should be discarded.
- 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 of mixing.
- Do not administer unless the solution is clear.
- Discard any unused remaining solution.
- Use in one patient on one occasion only.
- Contains no antimicrobial preservative.
- The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be selected by a physician.

Poison Schedule: Unscheduled.

Name and address of the sponsor:

Physioneal 40 is made by Baxter Healthcare SA, Ireland and supplied in Australia by
Baxter Healthcare Pty Ltd
1 Baxter Drive, Toongabbie, NSW 2146

AUST R 97418	AUST R 119077
AUST R 97426	AUST R 119078
AUST R 97431	AUST R 119079

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