מדיקל
טבע מדיקל בע"מ

רופא /ה, רוקח/ת נכבד/ה *ספטמבר 2012*
חברת טבע מודיעה על עדכון בעלון לרופא של המוצר הבא:

Physioneal 40 Glucose 1.36%, 2.27%, 3.86% פיזיוניל 40 גלוקוז תמיסה לדיאליזה
Solution for peritoneal dialysis

(Glucose, salts and water for peritoneal dialysis)

עדכון בעלון לרופא

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

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.

<u>Additions appear as underlined text and deletions as strikethrough:</u>

Posology and method of administration

<u>Administration</u>
<u>Physioneal 40 is intended for intraperitoneal administration only. Not for intravenous administration.</u>
<u>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.</u>
<u>Aseptic technique should be employed throughout the peritoneal dialysis procedure.</u>
<u>Do not administer if the solution is discoloured, cloudy, contains particulate matter or shows evidence of leakage, or if seals are not intact.</u>
<u>The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis.</u>
<u>For single use only.</u>
<u>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.</u>
<u>For further information on the use of the medicinal product see section 6.6 Instructions for use and handling.</u>

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).

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.

~~- 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.~~

Contraindications

Physioneal 40 should not be used in patients with (1) uncorrectable mechanical defects that prevent effective PD or increase the risk of infection, (2) documented loss of peritoneal function or extensive adhesions that compromise peritoneal function.

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

Special warnings and special 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, faecal fistula, colostomy or iliostomy, 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 paediatric 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 characterised 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 hyperkaelemia.

In situations in which there is a normal serum potassium level or hypokaelemia, the addition of potassium chloride (up to a concentration of 4 mEq/l) may be indicated to prevent severe hypokaelemia 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.

~~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:~~
~~serious conditions affecting the abdominal wall (e.g. skin infections or burns, recent surgery, hernia)~~
~~serious conditions affecting the abdominal cavity (e.g. ascites, ileus, adhesions, bowel perforation, diaphragmatic defects, tumours and advanced pregnancy – see section 4.6)~~
~~severe respiratory insufficiency,~~
~~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.~~

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

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: ≥10%; common: ≥1% and <10%; uncommon: ≥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 PCO2 increased	Common Uncommon

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

~~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).~~

Pharmacodynamic properties
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.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
~~In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.~~

Special precautions for storage
Store in the original package.

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

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 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. Refer to section 4.2.
Chemical and physical in-use stability has been demonstrated for 6 hours at 25°C for insulin (Actrapid 10 IU/L, 20 IU/L and 40 IU/L).
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.
The solution is free from bacterial endotoxins.

- ~~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.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות
http://www.health.gov.il, וניתן לקבלו מודפס ע"י פניה לחברת טבע.

טבע תעשיות פרמצבטיות בע"מ
רחוב התאנה 1,פארק התעשיות חמ"ן ת.ד. 975, שוהם 60850 | טל. 03-6864653 | פקס 03-6864944 |
www.tevapharm.com