SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Physioneal 40 Glucose 3.86% w/v / 38.6 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	56.6 g
equivalent to Glucose anhydrous	51.5 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 hydrogen carbonate	9.29 g
Sodium (S)-lactate solution equivalent to sodium (S)-lactate	6.73 g

After mixing

1000 ml of the mixed solution contains:	
Active substances:	
Glucose monohydrate	42.5 g
equivalent to Glucose anhydrous	38.6 g
Sodium chloride	5.38 g
Calcium chloride dihydrate	0.184 g
Magnesium chloride hexahydrate	0.051 g
Sodium hydrogen carbonate	2.10 g
Sodium (S)-lactate solution equivalent to sodium (S)-lactate	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 ($C_6H_{12}O_6$)	214 mmol/l
Na^+	132
Ca^{++}	mmol/l
Mg^{++}	1.25
Cl^-	mmol/l
HCO_3^-	0.25
$C_3H_5O_3^-$	mmol/l
	95 mmol/l
	25
	mmol/l
	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 hydrogen carbonate = 40 mmol/l).

3 PHARMACEUTICAL FORM

Solution for peritoneal dialysis.

Sterile, clear, colourless solution.

The pH of the final solution is 7.4.

Osmolarity: 483 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 hydrogen carbonate/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

Posology

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, 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.

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 population
The safety and efficacy of PHYSIONEAL 40 in paediatric patients have not been established. Therefore the clinical benefits of PHYSIONEAL 40 have to be balanced versus the risks of side effects in this patient category.
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.

Method of administration

Precautions to be taken before handling or administering the medicinal product

- 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 discoloured, 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.

- 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 instructions on the use of the medicinal product see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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

Use in patients with abdominal conditions

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 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)

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.

Peritonitis

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.

Hypersensitivity

Solutions containing glucose derived from hydrolysed maize starch should be used with caution in patients with a known allergy to maize or maize products. Hypersensitivity reactions such as those due to a corn (maize) 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.

Use in patients with elevated lactate levels

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, sepsis, 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.

General monitoring

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.

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.

Serum electrolyte concentrations (particularly hydrogen carbonate, potassium, magnesium, calcium and phosphate), blood chemistry (including parathyroid hormone and lipid parameters) and haematological parameters should be monitored periodically.

Metabolic alkalosis

In patients with plasma hydrogen carbonate level above 30 mmol/l, the risk of possible metabolic alkalosis should be weighed against the benefits of treatment with this product.

Secondary hyperparathyroidism

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.

Overinfusion

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.

Use of higher glucose concentrations

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. See section 4.9.

Addition of potassium

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.

Use in diabetic patients

In patients with diabetes, blood glucose levels should be monitored and the dosage of insulin or other treatment for hyperglycaemia should be adjusted.

Improper administration

Improper clamping or priming sequence may result in infusion of air into the peritoneal cavity, which may result in abdominal pain and/or peritonitis.

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.

Paediatric population

Safety and efficacy in paediatric patients have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

- 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 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of PHYSIONEAL 40 in pregnant women.

PHYSIONEAL 40 is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether PHYSIONEAL 40 metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from PHYSIONEAL 40 therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on fertility.

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 hydrogen carbonate 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: (≥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), not known (cannot be estimated from the available data)

System Organ Class	Preferred Term	Frequency
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Eosinophilia	Not known
METABOLISM AND NUTRITION 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 Not known Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Angioedema Rash	Not known Not known
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Musculoskeletal pain	Not known

System Organ Class	Preferred Term	Frequency
GENERAL DISORDERS AND ADMINISTRATION 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/ risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

See section 4.4 for information on overinfusion of Physioneal 40 and its treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peritoneal Dialytics, Hypertonic solutions

ATC code: B05DB

Mechanism of action

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.

Pharmacodynamic effects

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 hydrogen carbonate 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.

Clinical efficacy and safety

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 CO_2 and H_2O.

5.3 Preclinical safety data

No non-clinical studies have been performed with PHYSIONEAL 40.

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 6.3.

Aminoglycosides (eg. netilmycin, gentamycin, tobramycin) should not be mixed with penicillins due to chemical incompatibility.

6.3 Shelf life

- 2 years.
- After opening / dilution:

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.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store below 4°C.
For storage conditions of the reconstituted medicinal product, see section 6.3.

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 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
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
2.5 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
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
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 Luer connector + clamshell and minicap

6.6 Special precautions for disposal

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 Safety Moon seal (access seal) to allow administration of the mixed solution. The intraperitoneal solution must be infused within 24 hours after mixing. See section 4.2.

- 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.

- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

- In the case of damage, the container should be discarded.

- The solution is free from bacterial endotoxins.

7 MARKETING AUTHORISATION HOLDER

Vantive Limited
Wavertree Technology Park
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Liverpool, L7 9PE
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8 MARKETING AUTHORISATION NUMBER(S)

PL 58711/0019

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10 DATE OF REVISION OF THE TEXT

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