Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nutrineal PD4 1.1% Amino Acids Clear-Flex Solution for peritoneal dialysis

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Formula in mg/l	
Blend of Amino Acids:	
Alanine	951
Arginine	1071
Glycine	510
Histidine	714
Isoleucine	850
Leucine	1020
Lysine, HCl	955
Methionine	850
Phenylalanine	570
Proline	595
Serine	510
Threonine	646
Tryptophan	270
Tyrosine	300
Valine	1393
Sodium chloride	5380
Calcium chloride dihydrate	184
Magnesium chloride hexahydrate	51
Sodium (*S*)-lactate solution equivalent to Sodium (*S*)-lactate	4480
Composition in mmol/l	
Amino Acids	87.16
Na^+	132
Ca^{++}	1.25
Mg^{++}	0.25
Cl^-	105
$C_3H_5O_3^-$	40

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for peritoneal dialysis.
Nutrineal is a sterile, clear, colourless solution.

Osmolarity 365 mOsmol/l
pH at 25°C 6.6

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nutrineal is recommended as a non-glucose based peritoneal dialysis solution as part of a peritoneal dialysis regimen for the treatment of chronic renal failure patients. In particular, it is recommended for the malnourished peritoneal dialysis patients.

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 initiated and supervised by the prescribing physician.

Treatment should be re-evaluated after 3 months if there is no clinical or biochemical improvement in the status of the patient.

Adults: one peritoneal dialysis exchange per day of 2.0 l or 2.5 l is the recommended dose for a 70 kg body weight patient. In smaller patients the fill volume may need to be reduced depending on body size. In exceptional cases, a different posology may be indicated but the dose should not exceed two exchanges per day. Note that the recommended daily total intake of proteins is over or equal to 1.2 g/kg body weight for adult dialysis patients. 2.0 l of Nutrineal contains 22 g of amino acids which corresponds to 0.30 g/kg body weight/24 h (approximately 25% of the daily protein requirements) for an adult dialysis patient of 70 kg body weight.

Elderly: as for adults.

Children and adolescents: Safety and effectiveness in paediatric patients has not been established. If Nutrineal is used, the recommended posology is one peritoneal dialysis exchange per day. The clinical benefits of Nutrineal have to be balanced versus the risk of side effects in this patient category. For paediatric patients > 2 years old, a fill volume of 800 to 1400 ml/m2 to a maximum amount of 2000 ml, as tolerated, is recommended. Fill volumes of 200 to 1000 ml/m2 are recommended in children less than 2 years of age.

Method of administration

Nutrineal is intended for intraperitoneal administration only. Not for intravenous administration.

Peritoneal dialysis solutions may be warmed in the overpouch 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 due to an increased risk of contamination. Solutions should not be heated in a microwave oven due to the potential for damage to the solutions container and 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 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.

For single use only.

4.3 Contraindications

Nutrineal is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients listed in section 6.1,
- serum urea level above 38 mmol/L,
- uraemic symptoms,
- metabolic acidosis,
- inborn errors of amino acid metabolism,

- severe liver insufficiency,
- severe hypokalaemia,
- 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

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 Nutrineal.

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), broad-spectrum antibiotics may be indicated.

Hypersensitivity

If any sign or symptom of a suspected hypersensitivity reaction develop, intraperitoneal administration of Nutrineal should be stopped immediately. Appropriate therapeutic measures should be instituted as clinically indicated.

Metabolism of Nutrineal

A portion of the amino acids in Nutrineal is converted to metabolic nitrogenous waste, such as urea. If dialysis is insufficient, the additional metabolic waste generated by the use of Nutrineal may lead to the appearance of uraemic symptoms such as anorexia or vomiting. Symptoms can be managed by reduction of the number of Nutrineal exchanges, or discontinuation of Nutrineal or an increased dialysis dose with a non amino acid based solution.

Uncompensated metabolic acidosis and hyperammonemia
Particular care is indicated in cases of uncompensated metabolic acidosisand hyperammonemia. Metabolic acidosis and hyperammonemia should be corrected before and during Nutrineal treatment.

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 tumours, 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; and 2) other conditions including aortic graft placement and severe pulmonary disease.

General monitoring

Significant losses of medicinal products (including water soluble vitamins) may occur during peritoneal dialysis. Replacement therapy should be provided as necessary.

Dietary protein intake should be monitored.

Patients should be carefully monitored to avoid over- and underhydration. An accurate fluid balance record should be kept and the patient’s body weight monitored.

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

Overinfusion

Overinfusion of a peritoneal dialysis solution into the peritoneal cavity may be characterised by abdominal distension/abdominal pain and/or shortness of breath.

Treatment of peritoneal dialysis solution overinfusion is to drain the solution from the peritoneal cavity.

Addition of Potassium

Potassium is omitted from Nutrineal solutions due to the risk of hyperkalaemia.

- In situations in which there is a normal serum potassium level or hypokalaemia, 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 diabetic patients, blood glucose levels should be regularly monitored and the dosage of insulin or other treatment for hyperglycaemia should be adjusted.

Use in patients with secondary hyperparathyroidism

In patients with secondary hyperparathyroidism, the benefits and risks of the use of dialysis solution with low calcium content should be carefully considered as it might worsen hyperparathyroidism.

Paediatric population

Safety and effectiveness in paediatric patients has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with Nutrineal. Blood concentration of other dialysable medicinal products may be reduced during dialysis.

Plasma levels of potassium, calcium and magnesium 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 data from the use of Nutrineal in pregnant women.

No animal reproductive studies have been performed with Nutrineal (see section 5.3).

Nutrineal is not recommended during pregnancy and in women of childbearing potential not using contraception. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Nutrineal.

Lactation

It is unknown whether Nutrineal/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 Nutrineal 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 (e.g. Malaise, Hypovolaemia).

4.8 Undesirable effects

The adverse reactions within this section represent those that are thought to have an association with Nutrineal or in conjunction with performing the peritoneal dialysis procedure.

Undesirables effects which occurred in patients treated with Nutrineal from clinical trials and post marketing are listed below.

Frequency is based upon the following scale: 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); not known (cannot be estimated from the available data).

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
INFECTIONS AND INFESTATIONS	Infection	Common
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anaemia	Common
IMMUNE SYSTEM DISORDERS	Hypersensitivity	Not known
METABOLISM AND NUTRITION DISORDERS	Acidosis	Very common
	Hypervolaemia	Very common
	Hypokalaemia	Common
	Hypovolaemia	Common
	Anorexia	Very common
PSYCHIATRIC DISORDERS	Depression	Common
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnoea	Common
GASTROINTESTINAL DISORDERS	Vomiting*	Very common
	Nausea	Very common
	Gastritis	Very common
	Abdominal pain	Common
	Sclerosing encapsulating peritonitis	Not known
	Abdominal discomfort	Not known
	Peritonitis	Not known
	Peritoneal cloudy effluent	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritis	Not known
	Angioedema	Not known
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Asthenia	Very common
	Pyrexia	Not known

	Malaise	Not known
INVESTIGATIONS	Blood urea increased	Very common
	Peritoneal fluid analysis abnormal	Not known

*The term nausea and vomiting is not available in MedDRA 11.0. The term has been retained to reflect the available source data.

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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is potential for overdose resulting in hypervolaemia and electrolyte disturbances.

Management of Overdose:
- Hypervolaemia may be managed by using hypertonic peritoneal dialysis solutions and fluid restriction.
- Electrolyte disturbances may be managed according to the specific electrolyte disturbance verified by blood testing. 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 (see section 6.2).

Refer to section 4.4 on overinfusion of Nutrineal Clear-Flex and its treatmeant.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peritoneal dialytics, Hypertonic solutions, 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 balance.
This procedure is accomplished by administering peritoneal dialysis fluid through a catheter into the peritoneal cavity. Transfer of substances between the dialysis fluid and the patient's peritoneal capillaries is made across the peritoneal membrane according to the principles of osmosis and diffusion. After a few hours of 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 dialysing fluid.

Electrolyte concentration of the solution is basically the same as that of the physiological serum (except for lactate).

5.2 Pharmacokinetic properties

Intraperitoneally administered amino acids, buffer, electrolytes and water are absorbed into the blood and metabolised by the usual pathways.
70 % to 80 % of the amino acids infused are absorbed from the dialysis solution into the blood compartment after 4 to 6 hours of dwell in the peritoneal cavity.

5.3 Preclinical safety data

No non-clinical studies have been performed with Nutrineal. The amino acids contained in Nutrineal are substances which occur naturally in humans.

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, dilute (pH adjuster).
Water for Injections

6.2 Incompatibilities

Nutrineal PD4 in the Clear-Flex container should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

The product, once removed from the overpouch should be used immediately.

6.4 Special precautions for storage

Do not store below 4°C.

6.5 Nature and contents of container

The fluid is hermetically sealed inside a bag manufactured of co-extruded film (Clear-Flex) of polypropylene, polyamide and a blend of polypropylene, SEBS and polyethylene. On the outer layer of the film, a valve system is welded at the bottom of the bag (luer connector) and an injection site in the middle of the bag.

The bag is overwrapped inside a transparent overpouch made of multilayer copolymers.

Pack sizes:
Nutrineal is available in the following pack sizes:
2.5 1 3 units per box Single-bag
2.5 1 4 units per box Single-bag

6.6 Special precautions for disposal

For details on the conditions of administration see section 4.2.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for: Cefazolin (125 and 750 mg/l), ceftazidime (125 and 500 mg/l), aztreonam (250 and 1000 mg/l), fluconazole (40 and 80 mg/l), gentamicin (4 and 30 mg/l), tinzaparin (2500 IU/L), tobramycin (4 and 30 mg/l) or vancomycin (25 and 1500 mg/l).

From a microbiological point of view, unless the method of drug addition precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

- The intraperitoneal administration route requires the use of a specific catheter and an appropriate administration set which connects the solution container to the patient’s catheter.

- 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.
- In case of damage, the container should be discarded.
- Do not remove unit from overpouch until ready for use.
- Do not administer unless solution is clear.
- Discard any unused remaining solution.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
Caxton Way
Thetford, Norfolk
IP24 3SE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0167/086/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 3rd October 2007

10 DATE OF REVISION OF THE TEXT

May 2016