PRODUCT MONOGRAPH

NUTRINEAL™ PD4

1.1% Amino Acid Peritoneal Dialysis Solution

Peritoneal Dialysis Solution

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1.1% Amino Acid Peritoneal Dialysis Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Ingredients
Intraperitoneal	Solution, 1.1% Amino Acids	Histidine, Valine, Isoleucine, Alanine, Leucine, Arginine, Lysine, Glycine, Methionine, Proline, Phenylalanine, Serine, Threonine, Tyrosine, Tryptophan, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Sodium Chloride, Sodium Lactate, Hydrochloric acid (for pH adjustment), Water for Injection.

INDICATIONS AND CLINICAL USE

Nutrineal™ PD4 is indicated for the treatment of protein malnutrition in peritoneal dialysis patients.

CONTRAINDICATIONS

Nutrineal™ PD4 is contraindicated in patients with:

- known hypersensitivity to any amino acids in the product or to any of the excipients or components of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- serum urea level above 38 mmol/L
- uremic symptoms
- metabolic acidosis
- inborn errors of amino acid metabolism
- liver insufficiency
- severe hypokalemia
- uncorrectable mechanical defects that prevent effective peritoneal dialysis or increase the risk of infection
- documented loss of peritoneal function or extensive adhesions that compromise peritoneal function

WARNINGS AND PRECAUTIONS

Warnings

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™ PD4.

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) wherever possible. Prior to identification of the involved organism(s), broad-spectrum antibiotics may be indicated.

If any signs or symptoms of a suspected hypersensitivity reaction develop, intraperitoneal administration of Nutrineal™ PD4 must be stopped immediately. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Precautions

General

Nutrineal™ PD4 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 not intact.

The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis.

Protein, amino acids, water-soluble vitamins, and other medicines may be lost during peritoneal dialysis and may require replacement.

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 or colostomy, 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.

Overinfusion of a peritoneal dialysis solution into the peritoneal cavity may be characterized 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.

Potassium is omitted from Nutrineal™ PD4 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[1] and should be made after careful evaluation of serum and total body potassium, only under the direction of a physician.

Additives may be incompatible. See DOSAGE & ADMINISTRATION.

Carcinogenesis and Mutagenesis

Long-term animal studies with Nutrineal™ PD4 have not been performed to evaluate the carcinogenic or mutagenic potential.

Renal

Use of Nutrineal™ PD4 can result in elevation of blood urea nitrogen (BUN), uremic signs and symptoms, metabolic acidosis, nausea and vomiting.

Particular care is indicated in cases of uncompensated metabolic acidosis, severe liver dysfunction and hyperammonemia. Metabolic acidosis should be corrected before and during Nutrineal™ PD4 treatment.

A portion of the amino acids in Nutrineal™ PD4 is converted to metabolic nitrogenous waste, such as urea. If dialysis is insufficient, the additional metabolic waste generated by the use of Nutrineal™ PD4 may lead to the appearance of uremic symptoms such as anorexia or vomiting. Symptoms can be managed by discontinuation of Nutrineal™ PD4 or an increased dialysis dose with a non amino acid based solution.

Metabolic acidosis may be treated with an oral source of alkali (such as sodium bicarbonate, calcium carbonate, or calcium acetate).

Sexual Function/Reproduction

Long-term animal studies with Nutrineal™ PD4 have not been performed to evaluate the effect on fertility.

Special Populations

Pregnant or Nursing Women: There are no adequate data from the use of Nutrineal™ PD4 in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Nutrineal™ PD4.

Pediatrics: Safety and effectiveness in pediatric patients have not been established.

Monitoring and Laboratory Tests

In patients using cardiac glycosides, plasma level of potassium, calcium and magnesium must be

carefully monitored.

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

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse reactions within this section represent those that are thought to have an association with Nutrineal™ PD4 or in conjunction with performing the peritoneal dialysis procedure.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials the following Adverse Events were observed in ≥5% of patients receiving Nutrineal™ PD4. Adverse events are presented in the table if the incidence of the adverse event was ≥2% higher compared to the control group.

Clinical Trial Adverse Events

System Organ Class (SOC)	Preferred MedDRA Term	Frequency	Percentage of Patients
INFECTIONS AND INFESTATIONS	Catheter site infection Infection	Common Common	8.9 5.1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anemia	Common	6.3
METABOLISM AND NUTRITION DISORDERS	Acidosis Hypervolemia Hypokalemia Hypovolemia	Very Common Very Common Common Common	35.4 13.9 8.9 6.3
PSYCHIATRIC DISORDERS	Depression	Common	5.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea	Common	6.3
GASTROINTESTINAL DISORDERS	Nausea/Vomiting*	Very Common	19.0

	Anorexia Nausea Gastritis	Very Common Very Common Common	15.2 15.2 5.1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Asthenia	Very Common	10.1
INVESTIGATIONS	Blood urea increased	Very Common	15.2

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

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported in the post-marketing experience.

INFECTIONS AND INFESTATIONS: Peritonitis bacterial

IMMUNE SYSTEM DISORDERS: Hypersensitivity

METABOLISM AND NUTRITION DISORDERS: Anorexia

GASTROINTESTINAL DISORDERS: Abdominal pain, Peritonitis, Peritoneal cloudy effluent, Abdominal discomfort

SKIN AND SUBCUTANEOUS DISORDERS: Angioedema, Pruritus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Catheter related complication, Pyrexia, Malaise

INVESTIGATIONS: Peritoneal fluid analysis abnormal

DRUG INTERACTIONS

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

There is no incompatibility between heparin or insulin and Nutrineal™ PD4 in the VIAFLEX® container.

In case of medicinal product admixture, compatibilities must be checked before use and admixed solution must be used immediately.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Nutrineal™ PD4 (1.1% Amino Acid Peritoneal Dialysis Solution) is intended for intraperitoneal administration only, substituting for one or two of the dextrose containing exchanges per day, as part of the daily dialysis regimen for patients with protein malnutrition. Adequate dialysis should be established prior to initiation of treatment with Nutrineal™ PD4.

Adults and Elderly:

- One peritoneal dialysis (Nutrineal™ PD4) exchange per day of one 2.0 1iter or one 2.5 1iter bag 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 regimen may be indicated but the dose should not exceed two exchanges per day.
- Note that the recommended daily total intake of proteins is greater than or equal to 1.2 g/kg body weight for adult dialysis patients. A 2.0 1iter bag of Nutrineal™ PD4 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.

Children and Adolescents:

- Safety and effectiveness in pediatric patients has not been established. If Nutrineal™ PD4 is used, the recommended dose is one peritoneal dialysis exchange per day. The risk/benefit ratio should be assessed and the dialysis prescription and appropriate adaptation of fill volume, must be individualized.

Administration

Nutrineal™ PD4 is intended for intraperitoneal administration only. Not for intravenous administration.

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.

In case of medicinal product admixture, compatibilities must be checked before use and the admixed solution must be used immediately.

Peritoneal dialysis solutions may be warmed in the overpouch to 37°C (98.6°F) 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.

Do not administer unless the solution is clear and free of particulate matter.

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.

Directions for Use

Aseptic technique should be employed throughout the peritoneal dialysis procedure. For complete system preparation, see directions accompanying ancillary equipment.

Preparation and Administration for the Single Bag Container

Follow the instructions in user manual or directions accompanying tubing sets and devices for automated peritoneal dialysis.

Preparation and Administration for the TWIN BAG® Container

1. Do not remove from the carton until ready for use.
2. Remove container from overpouch.
3. Inspect solution container and frangible to ensure that there are no leaks, and the solution has not expired. If leaks are detected, or the expiration date has lapsed, discard container.
4. Inspect the patient connector to ensure the pull ring is attached. Do not use if pull ring is not attached to the connector.
5. Inspect tubing and drainage container for presence of solution. If solution is noted, discard unit. NOTE: Small water droplets are acceptable.
6. Ensure patient transfer set is closed.
7. Break frangible at patient connector.
8. Remove pull ring from the patient connector.
9. Remove disconnect cap from patient transfer set. ***Immediately*** attach patient transfer set connector to the patient connector by twisting the connector until firmly secured.
10. Clamp new bag solution line.
11. Break frangible at container port.
12. Hang the new solution container.
13. Place the drainage container below the level of the peritoneum.

Proceed with either Procedure A or Optional: Procedure B

Procedure A

14. Open transfer set clamp to drain solution from the peritoneal cavity.
15. Close transfer set line clamp after drainage is complete.
16. Open new solution line clamp and allow the new solution to flow into the drainage container for five seconds.
17. Clamp drain line.
18. Open transfer set clamp and allow the solution to flow into the peritoneal cavity.
19. Close transfer set clamp when infusion is complete.
20. Open a new disconnect cap following the directions accompanying the cap.

21. Disconnect the patient transfer set from the TWIN BAG® set and attach the new disconnect cap to the transfer set.

Optional: Procedure B

14. Open new solution line clamp and allow the new solution to flow into the drainage container for five seconds.
15. Clamp new solution line.
16. Open transfer set clamp to drain solution from the peritoneal cavity.
17. Clamp drain line.
18. Open new solution line and allow solution to flow into the peritoneal cavity.
19. Close transfer set clamp when infusion is complete.
20. Open a new disconnect cap following the directions accompanying the cap.
21. Disconnect the patient transfer set from the TWIN BAG® set and attach the new disconnect cap to the transfer set.

In the Event That Supplemental Medication is Prescribed

1. Inspect container to ensure resealable rubber medication port is in place. Discard if rubber medication port is not attached to container port.
2. Prepare medication port according to aseptic technique.
3. Using a syringe with a one-inch long, 19 to 25 gauge needle, puncture resealable medication port and inject medication.
4. Position container with medication port facing upward. Squeeze and tap medication port to empty solution. Mix solution by vigorously agitating container.

OVERDOSAGE

For the management of suspected overdose, contact your regional poison control centre.

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

Management of Overdose:

- Hypervolemia 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, hypokalemia, 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Peritoneal dialysis is a procedure which utilizes the body's peritoneal membrane as a natural filter for removing toxic substances and metabolites normally excreted by the kidneys, and for aiding in the regulation of fluid, electrolyte, and acid-base balance[3].

While in conventional peritoneal dialysis solutions the osmotic agent is dextrose[4], in Nutrineal™ PD4 (1.1% Amino Acid Peritoneal Dialysis Solution), the osmotic agent is a mixture of essential and nonessential amino acids with a total concentration of 1.1% (11 g/L). Electrolyte concentrations in the dialysis solution have been formulated to normalize plasma electrolyte concentrations; lactate is present as a bicarbonate precursor[5]. The amino acids in Nutrineal™ PD4 provide an osmotic gradient similar to peritoneal dialysis solutions with 1.5% dextrose. The calculated osmolarity of Nutrineal™ PD4 is 365 mOsmol/L, whereas the calculated value for peritoneal dialysis solutions with 1.5% dextrose (e.g., Dianeal® PD-2 Peritoneal Dialysis Solution) is 346 mOsmol/L. Nutrineal™ PD4 is therefore an effective alternate osmotic agent.

The amino acid mixture is composed of 64% essential and 36% nonessential amino acids by weight. Some of the nonessential amino acids (i.e., tyrosine, serine, arginine) are included in the solution specifically because their biosynthesis from other substrates may be impaired in dialysis patients[6]. The amino acids in Nutrineal™ PD4 are absorbed into the blood and are substrates for synthesis of proteins, both constituent and functional.

Many patients with chronic renal failure display evidence of protein or protein-calorie malnutrition related to reduced protein and energy intake and increased protein and energy requirements. During conventional peritoneal dialysis with dextrose-based solutions, there is an expected loss of amino acids and proteins into the spent dialysate[7]. Nutrineal™ PD4 provides amino acids in the dialysis solution to compensate for unavoidable losses of protein and amino acids into the dialysate. This improves abnormal plasma amino acid profiles frequently observed in patients in chronic renal failure. The maintenance of adequate nutrition in peritoneal dialysis patients has been found to reduce the incidence of peritonitis and to minimize the length of hospitalization. Since one of the complications of renal failure is decreased ability to eliminate phosphate, Nutrineal™ PD4 provides a biologically utilizable phosphate free source material for protein synthesis.

Pharmacodynamics

Nutrineal™ PD4 is a sterile and non-pyrogenic solution which when used in peritoneal dialysis enables the removal of toxic substances produced by nitrogen metabolism and normally excreted by the kidneys, and facilitates the regulation of fluid and electrolytes as well as acid base balance.

The concentration of electrolytes in the fluid is similar, except for lactate, to the electrolyte composition of normal extra-cellular fluid.

Pharmacokinetics

The solution is instilled in the peritoneal cavity, and then drained after a dwell time as prescribed by the physician. The solution takes effect across the peritoneal membrane according to the principles of osmotic diffusion. Seventy to eighty percent (70 – 80%) of the amino acids infused are absorbed after 4 – 6 hours of dwell in the peritoneal cavity.

Electrolytes follow the standard metabolism of each ion.

STORAGE AND STABILITY

Protect from light until ready to use. Exposure of pharmaceutical products to heat should be minimized. Store at 15-25°C. Do not remove from carton until ready to use.

The plastic TWIN BAG® solution container system is fabricated from polyvinyl chloride (PL-146 Plastic). Exposure to temperatures above 30°C during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. The amount of water that can permeate from inside the solution container into the overpouch is insufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

SPECIAL HANDLING INSTRUCTIONS

See STORAGE AND STABILITY.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Nutrineal™ PD4 is a sterile, nonpyrogenic solution of essential and nonessential amino acids and electrolytes supplied in Baxter Corporation's PL-146 container system.

Nutrineal™ PD4 is for intraperitoneal administration only and contains no bacteriostatic or antimicrobial agents.

Each 100 mL of Nutrineal™ PD4 contains:

Essential Amino Acids	
Histidine, USP	71.4 mg
Isoleucine, USP	84.9 mg
Leucine, USP	101.9 mg
Lysine (added as Lysine-HCl), USP	95.5 mg
Methionine, USP	84.9 mg
Phenylalanine, USP	57 mg
Threonine, USP	64.5 mg
Tryptophan, USP	27 mg
Valine, USP	139.3 mg
Nonessential Amino Acids	
Alanine, USP	95.1 mg
Arginine, USP	107.1 mg
Glycine, USP	50.9 mg
Proline, USP	59.5 mg

Serine, USP	50.9 mg
Tyrosine, USP	30 mg
Electrolytes	
Calcium Chloride Dihydrate, USP	18.3 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Sodium Chloride, USP	538 mg
Sodium Lactate	448 mg
Excipients	
Water for Injection, USP	qs
Hydrochloric acid (for pH adjustment)	qs
Concentration of ions	
Amino Acids	87 mmol/L
Sodium	132 mmol/L
Calcium	1.25 mmol/L
Magnesium	0.25 mmol/L
Chloride	105 mmol/L*
Lactate	40 mmol/L

*Includes additional contributions from lysine hydrochloride and hydrochloric acid used for pH adjustment.

pH (adjusted with hydrochloric acid): 6.6 (5.7 to 6.8)
Calculated osmolarity: approx. 365 mOsm/L.

Nutrineal™ PD4 is available in TWIN BAG® containers holding 2000 mL or 2500 mL and Single Bag containers holding 2500 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	Chemical Name	Molecular Formula	Molecular Mass
L-Alanine	2-Aminopropanoic acid	$C_3H_7NO_2$	89.09
L-Arginine	2-Amino-5-guanidinopentanoic acid	$C_6H_{14}N_4O_2$	174.2
Glycine	Aminoethanoic acid	$C_2H_5NO_2$	75.07
L-Histidine	2-Amino-3-(1*H*-imidazol-4-yl)-propanoic acid	$C_6H_9N_3O_2$	155.16
L-Isoleucine	2-Amino-3-methylpentanoic acid	$C_6H_{13}NO_2$	131.17
L-Leucine	2-Amino-4-methylpentanoic acid	$C_6H_{13}NO_2$	131.18
L-Lysine HCl	2,6-Diaminohexanoic acid	$C_6H_{14}N_2O_2$	182.65
L-Methionine	2-Amino-4-(methylthio)butanoic acid	$C_5H_{11}NO_2S$	149.21
L-Phenylalanine	2-Amino-3-phenylpropanoic acid	$C_9H_{11}NO_2$	165.19
L-Proline	Pyrrolidine-2-carboxylic acid	$C_5H_9NO_2$	115.13
L-Serine	2-Amino-3-hydroxypropanoic acid	$C_3H_7NO_3$	105.1
L-Threonine	2-Amino-3-hydroxybutanoic acid	$C_4H_9NO_3$	119.12
L-Tryptophan	2-Amino-3-(l*H*-indol-3-yl)-propanoic acid	$C_{11}H_{12}N_2O_2$	204.23
L-Tyrosine	2-Amino-3-(4-hydroxyphenyl)-propanoic acid	$C_9H_{11}NO_3$	181.19
L-Valine	2-Amino-3-methylbutanoic acid	$C_5H_{11}NO_2$	117.15
Calcium Chloride Dihydrate	Calcium Chloride Dihydrate	$CaCl_2 \bullet 2H_2O$	147.01
Magnesium Chloride Hexahydrate	Magnesium chloride hexahydrate	$MgCl_2 \bullet 6H_20$	203.30
Sodium Chloride	Sodium chloride	NaCl	58.44
Sodium Lactate	Sodium 2-hydroxypropanoate	$C_3H_5NaO_3$	112.07

DETAILED PHARMACOLOGY

Nutrineal™ PD4 (1.1% Amino Acid Peritoneal Dialysis Solution) contains a mixture of amino acids, lactate, and electrolytes (sodium, chloride, calcium, and magnesium), which are currently used in approved parenteral nutrition solutions and peritoneal dialysis solutions. The amino acids in Nutrineal™ PD4 are not new chemical entities, but are naturally occurring compounds whose distribution and metabolism are well known, and whose urinary excretion is negligible in patients with end stage renal disease (ESRD)[8]. Due to the volume of information concerning amino acid use in humans (orally and parenterally), and the long history of research on amino acids, the nonclinical pharmacology, pharmacokinetic, and toxicology studies traditionally done

as part of new drug development have not been conducted as part of the development program for Nutrineal™ PD4. Several pharmacology and nonclinical toxicology studies have been conducted with Nutrineal™ PD2. In addition, several nonclinical studies have been conducted with other peritoneal dialysis solutions or intravenous solutions that are similar in composition to Nutrineal™ PD4 and provide valuable supporting data on the safety of amino acid based peritoneal dialysis solutions. All solution formulations are presented in Table 1.

Table 1 - Quantitative Composition of Nutrineal™ PD4 Compared to Other Peritoneal Dialysis Solutions and Intravenous Solutions (g/litre)

Ingredient	Formulation (Method of Administration)					
	3%EAA[1] (iv)	5%SAAS[2] (iv)	1%AA + PD2[3] (ip)	2%AA + PD2[3] (ip)	Nutrineal™ PD2 (ip)	Dianeal® PD2 w/dextrose[4] (ip)
Total amino acids	30	50	10	20	11	none
L-alanine	none	10.4	0.88	1.76	0.95	none
L-arginine	none	5.2	0.48	0.96	1.07	none
L-glycine	1.4	10.4	0.46	0.92	0.51	none
L-histidine	2	2.2	0.62	1.24	0.71	none
L-leucine	4.4	3.1	1.28	2.56	1.02	none
L-isoleucine	2.8	2.4	0.76	1.52	0.85	none
L-lysine*	3.2	2.9	0.85	1.70	0.76	none
L-methionine	4.4	2.9	0.58	1.16	0.85	none
L-phenylalanine	4.8	3.1	0.35	0.70	0.57	none
L-proline	none	2.1	0.54	1.08	0.59	none
L-serine	none	none	0.47	0.94	0.51	none
L-threonine	2	2.1	0.89	1.78	0.65	none
L-tryptophan	1	0.9	0.19	0.38	0.27	none
L-tyrosine	0.2	0.2	0.35	0.70	0.30	none
L-valine	3.2	2.3	1.15	2.30	1.39	none
L-cystine	none	none	none	none	none	none
L-glutamic acid	none	none	none	none	none	none
L-aspartic acid	none	none	none	none	none	none
Dextrose	none	none	none	none	none	15 or 42.5
Dibasic potassium phosphate	none	2.61	none	none	none	none
Calcium chloride dihydrate	none	none	0.257	0.257	0.257†	0.257
Magnesium chloride hexahydrate	none	0.051	0.051	0.051	0.051	0.051
Sodium acetate	none	3.4	none	none	none	none
Sodium lactate	none	none	4.48	4.48	4.48	4.48
Sodium chloride	none	0.585	5.38	5.38	5.38	5.38

EAA = essential amino acids; SAAS = synthetic amino acid solution; AA = amino acids; iv = intravenous;ip=intraperitoneal

[1]Solution used in Study No. R.D. 01-101, CC1101B

[2]Solution used in Study No. R.D. 1-101A, CC1101A

[3]Solution used in Study No. RO62830524

[4]Solution used in Study No. RO62830524 contained 42.5 g/L dextrose

*Lysine added to the formulation as lysine HCl but analytically measured and reported as lysine

†Nutrineal PD4 (with 1.1% amino acids) has 0.183 g/L calcium chloride dihydrate

The amino acids and electrolytes contained in Nutrineal™ PD4 are present naturally in the foods consumed by humans. These ingredients have been tested in numerous biological systems and been the focus of biological research for several centuries. In foods, amino acids are chemically bonded together to form proteins. After oral ingestion, the proteins are hydrolyzed to amino acids in the digestive tract and these are then absorbed into the portal blood stream. During intraperitoneal administration, the amino acids from Nutrineal™ PD4 are absorbed across the peritoneal membrane and are transported via the portal circulation first through the liver and then out into the peripheral tissues. Nutritional studies conducted during the period of approximately 1900-1960 defined the amino acid requirements for various species, the metabolic processes by which the body handles them, and their acceptable levels of intake. The composition of Nutrineal™ PD4 is based on this well-established data.

In a controlled clinical study in an outpatient setting (Baxter Clinical Study No. RD-92-CA-042), there was a statistically significant ($p<0.05$) overall improvement in nutritional status over a three month study period among the Nutrineal™ PD2 treated patients compared to the control patients, based on the proportion of patients showing improvement from baseline in two or more of the five efficacy parameters (e.g., albumin, prealbumin, total protein, transferrin, and mid-arm muscle circumference). The proportion of patients showing overall improvement was 70% for the Nutrineal™ PD2 group and 45% for the control group. The difference in nutritional status between the Nutrineal™ PD2 patients and the control patients was most pronounced at month 1; differences between the two groups were significant ($p\leq 0.056$ or well below) for all four parameters (albumin, prealbumin, total protein, and transferrin) measured.

Additionally, analysis of insulin-like growth factor-1 (IGF-1), another indicator of nutritional status, showed a statistically significant ($p<0.003$) difference between the Nutrineal™ PD2 and control patients at month 3.

The peritoneal equilibration test (PET), which measures the transport characteristics of the peritoneal membrane, showed no statistical or clinically significant differences between the Nutrineal™ PD2 and control groups in ultrafiltration volume or peritoneal membrane mass transfer area coefficients for glucose, urea, creatinine, and total protein after three months, as well as at six months in eight patients who received Nutrineal™ PD2 for that long. Therefore, the use of Nutrineal™ PD2 for up to six months had no deleterious effects on the peritoneal membrane.

In an uncontrolled clinical study in an outpatient setting using Nutrineal™ PD4 with 2.5 mEq/L calcium electrolyte concentration (Baxter Clinical Study No. PRO-NIV-AO-048C), statistically significant increases in serum albumin ($p<0.01$) and transferrin ($p<0.05$) were observed at month 3 (end of treatment).

In a 35 day controlled metabolic balance study in patients with protein calorie malnutrition (Baxter Clinical Study No. DT88002), a significant improvement in nitrogen balance occurred during the use of Nutrineal™ PD2. The significant improvement in nitrogen balance was accompanied by statistically significant increases in serum total protein and serum transferrin, increases in serum albumin and a trend toward normalization of plasma amino acids.

Significant decreases from baseline were observed for both phosphorus (p=0.050 and 0.006, respectively) and potassium (p=0.045 and 0.031, respectively) in the 35 day metabolic balance study and in a controlled, three month outpatient study. Clinical research has shown that phosphorus and potassium balances usually change in parallel with nitrogen balance. In the absence of significant dietary changes, serum concentrations of potassium and phosphorus decrease when nitrogen balance increases.

To evaluate the amount of amino acids taken up from Nutrineal™ PD2, dialysate amino acid concentrations and dialysate effluent volumes were measured at the end of a 4-hour exchange with Nutrineal™ PD2 on the 1st, 9th and 19th days of treatment. Net absorption was obtained by subtracting the mass remaining at four hours (volume multiplied by concentration) from the mass infused (volume infused multiplied by concentration in Nutrineal™ PD2). Percent net absorption (percent uptake) was calculated as the mass absorbed divided by the mass infused multiplied by 100%.

The results are shown in Table 2. The mean percent net absorption (or percent uptake) at four hours ranged from 77% for lysine and histidine to 85% for methionine. This value for any amino acid was essentially the same on all three days in which it was assessed. The reproducibility of these numbers attests to the lack of any effect of the solution upon the transport characteristics of the peritoneal membrane.

The total grams of amino acids absorbed can be calculated from the data in Table 2 and the amino acid content of Nutrineal™ PD2, as shown in Table 3. The percent net absorption of amino acids over a four hour exchange was (17.53/22.00)x100% equals 79.7%, or approximately 80%.

Table 2 - Mean Percent Net Absorption of Amino Acids*

Amino Acid	**Day of Treatment with Nutrineal™ PD2 [Day of Study]**		
	1 [16]	**9 [26]**	**19 [35]**
Histidine	77	76	77
Isoleucine	83	81	83
Leucine	84	82	84
Lysine	77	74	76
Methionine	85	84	85
Phenylalanine	79	77	78
Threonine	80	78	80
Tryptophan	80	78	79
Valine	80	78	79
Tyrosine	78	76	78
Alanine	81	79	81
Arginine	78	76	77
Glycine	81	79	81
Proline	79	76	79
Serine	82	80	82

*Results from Baxter Clinical Study No. DT88002

Table 3 - Net Amino Acid Absorption during a 4-hr Exchange with Nutrineal™ PD2

Amino Acid	g/2 L	% Net Absorption*	g Absorbed
Histidine	1.42	77	1.09
Isoleucine	1.70	82	1.40
Leucine	2.04	83	1.70
Lysine	1.52	76	1.15
Methionine	1.70	85	1.44
Phenylalanine	1.14	78	0.89
Threonine	1.30	79	1.03
Tryptophan	0.54	79	0.43
Valine	2.78	79	2.20
Tyrosine	0.60	77	0.46
Alanine	1.90	80	1.53
Arginine	2.14	77	1.65
Glycine	1.02	80	0.82
Proline	1.18	78	0.92
Serine	1.02	81	0.83
Total	22.00		17.53

*Mean of Days 16, 26, and 35

The percent absorption was directly correlated with the dialysate/plasma (D/P) creatinine ratio, a measure of membrane transport characteristics for small molecules measured by a specific protocol in a four-hour peritoneal solute equilibration test. The D/P ratio is a measure of the extent to which equilibration between blood and dialysate is achieved over four hours, and this quantity varies from patient to patient. The data indicate that, in general, absorption of amino acids from the peritoneal cavity in an individual patient was governed by the transport properties of that patient's peritoneal membrane. Generally, the higher the D/P ratio, the higher the percent amino acid uptake. A similar relationship exists between D/P creatinine and the dextrose absorption from the dextrose-based dialysis solutions.

The percent net absorption of amino acids from Nutrineal™ PD2 is essentially the same as that found in studies with other similar amino acid peritoneal dialysis solutions. The studies reported that amino acids are rapidly absorbed from the peritoneal cavity during dialysis with such a solution and that there is, on the average, net absorption of 70 - 90% of the amino acids infused intraperitoneally during a 4 - 6 hour dwell.

The acute effect of Nutrineal™ PD2 on plasma amino acid concentrations was assessed by sampling plasma before and at the end of a four-hour morning exchange with Nutrineal™ PD2. Pre- and post-exchange plasma amino acid concentrations for Day 16, which was the first day in which patients received Nutrineal™ PD2, are shown in Table 4. Overall, the mean increase in amino acid concentration above pre-exchange for the amino acids included in the solution was about 63% at the end of the four-hour exchange. The increases ranged from 21% for lysine to 196% for methionine. The table also includes increases or decreases in concentrations of amino acids that were not present in Nutrineal™ PD2.

Table 4 - Pre- and Post- Exchange Plasma Amino Acid Concentrations (Day 16) During Treatment with Nutrineal™ PD2*

	Pre-Exchange N=21	Post-Exchange (percent change from baseline) N=21	p-value Pre vs. Post
Essential Amino Acids			
Histidine	66 ± 12[a]	91 ± 17 (38)	<0.01
Isoleucine	59 ± 14	105 ± 28 (78)	<0.01
Leucine	86 ± 20	126 ± 33 (45)	<0.01
Lysine	160 ± 32	194 ± 31 (21)	<0.01
Methionine	24 ± 10	71 ± 23 (196)	<0.01
Phenylalanine	56 ± 17	83 ± 19 (48)	<0.01
Threonine	117 ± 34	166 ± 44 (42)	<0.01
Tryptophan	20 ± 11	26 ± 13 (30)	<0.05
Valine	141 ± 30	341 ± 82 (142)	<0.01
Semi-Essential Amino Acids			
Cystine	59 ± 24	62 ± 26 (5)	NS
Tyrosine	34 ± 10	43 ± 13 (26)	<0.01
Nonessential Amino Acids			
Alanine	394 ± 130	472 ± 143(20)	<0.01
Arginine	79 ± 20	118 ± 28(49)	<0.01
Asparagine	45 ± 11	43 ± 20 (-4)	NS
Aspartic acid	14 ± 6	14 ± 8 (0)	NS
Citrulline	88 ± 25	99 ± 26 (12)	<0.01
Glutamic acid	53 ± 22	51 ± 28 (-4)	NS
Glutamine	674 ± 129	677 ± 127 (1)	NS
Glycine	341 ± 135	338 ± 131 (-3)	NS
Ornithine	53 ± 12	86 ± 19 (62)	<0.01
Proline	181 ± 45	279 ± 74 (54)	<0.01
Serine	69 ± 18	86 ± 25 (25)	<0.01
Taurine	69 ± 30	62 ± 26 (-10)	<0.01
Hydroxyproline	37 ± 12	40 ± 13 (8)	NS
α-Aminobutyrate	7 ± 5	11 ± 4 (57)	<0.01

* Results from Baxter Clinical Study No. DT88002.

[a] Mean standard deviation; units are μmol/L

It is also known from previous studies in the literature that amino acids absorbed from the peritoneal cavity appear rapidly in blood, with a peak in concentration at one to two hours after instillation of the solution into the peritoneal cavity. It may be presumed that much of the absorption is through the visceral peritoneum via the mesenteric vessels to the liver, i.e., similar to the physiologic route of delivery of diet-derived amino acids through the gut and via the portal vein. After the maximum is reached the concentration declines rapidly, but remains above pre-exchange concentrations at four hours. In Study No. DT88002, which also evaluated the blood concentration of amino acids pre-exchange and 4 hours post-Nutrineal™ PD2 exchange, it was determined that all amino acids originally present in the solution, except glycine, were greater post-exchange when compared to pre-exchange blood concentrations (Table 4). Similarly, other amino acids/metabolites, such as cystine and ornithine, were also greater post-Nutrineal™ PD2 exchange, as compared to pre-exchange concentrations. These increases may also reflect the

effect of amino acids absorbed from food proteins, as patients ate during the early portion of the exchange.

The effects of treatment with Nutrineal™ PD2 on the amino acid profile during the 20 days of treatment were also investigated. Plasma samples were obtained on Day 16 (prior to the first instillation of Nutrineal™ PD2 on the first day of treatment, Day 26 (after ten days of treatment), and Day 35 (on the 20th day of treatment). The results are shown in Table 5. Between Days 16 and 26, there were significant increases in histidine, lysine, threonine, valine, cystine, arginine, citrulline, ornithine, and proline and a decrease in taurine. Between Days 26 and 35, there was a further increase in cystine and a further decrease in taurine.

Table 5 - Pre-exchange Plasma Amino Acid Concentrations* during Treatment with Nutrineal™ PD2

	Day 16 N=21	**Day 26 N=19**	**Day 35 N=18**	**Normals****
Essential Amino Acids				
Histidine	66 ± 12†	76 ± 14[a]	75 ± 13[a]	88 ± 10
Isoleucine	59 ± 14	60 ± 10	56 ± 11	64 ± 16
Leucine	86 ± 20	89 ± 18	89 ± 21	127 ± 27
Lysine	160 ± 32	173 ± 39[a]	174 ± 31[b]	197 ± 38
Methionine	24 ± 10	22 ± 4	23 ± 4	28 ± 5
Phenylalanine	56 ± 17	53 ± 19	56 ± 16	56 ± 9
Threonine	117 ± 34	132 ± 36[a]	136 ± 40[b]	155 ± 41
Tryptophan	20 ± 11	21 ± 11	21 ± 12	NA
Valine	141 ± 30	187 ± 30[a]	186 ± 42[a]	232 ± 51
Semi-Essential Amino Acids				
Cystine	59 ± 24	63 ± 20[a]	68 ± 23[a,c]	61 ± 10
Tyrosine	34 ± 10	35 ± 12	34 ± 8	62 ± 13
Nonessential Amino Acids				
Alanine	394 ± 130	402 ± 128	414 ± 155	433 ± 166
Arginine	79 ± 20	95 ± 23[a]	93 ± 19[a]	99 ± 22
Asparagine	45 ± 11	44 ± 11	45 ± 10	48 ± 13
Aspartic Acid	14 ± 6	16 ± 7	14 ± 7	6 ± 3
Citrulline	88 ± 25	98 ± 26[a]	98 ± 29[a]	46 ± 22
Glutamic Acid	53 ± 22	40 ± 19	46 ± 26	39 ± 2
Glutamine	674 ± 129	689 ± 123	660 ± 92	480 ± 133
Glycine	341 ± 135	288 ± 102	318 ± 119	265 ± 118
Ornithine	53 ± 12	62 ± 18[a]	59 ± 15[b]	66 ± 28
Proline	181 ± 45	203 ± 47[b]	205 ± 55[b]	210 ± 65
Serine	69 ± 18	71 ± 14	71 ± 12	108 ± 24
Taurine	69 ± 30	55 ± 23[b]	45 ± 20[a,c]	48 ± 18
Hydroxyproline	37 ± 12	33 ± 13	35 ± 13	16 ± 13
α-Aminobutyrate	7 ± 5	11 ± 4[a]	10 ± 6	NA

* Results from Baxter Clinical Study No. DT88002

† Mean ± standard deviation; units are in μmol/L

[a,b] Differs from Day 16, P<0.01 and P<0.05, respectively

[c] Differs from Day 26, P<0.05

NA Not Available

** Data from 12 normal subjects with normal renal function obtained from Central Amino Acid Laboratory, University of Iowa

In Study No. RD-92-CA-042, the chronic effects of Nutrineal™ PD2 on the plasma amino acid profile were compared to those with dextrose Dianeal®. Over a three month treatment period, patients in the Nutrineal™ PD2-treated group showed significant increases in pre-exchange plasma concentrations of histidine, threonine, valine, ornithine, and serine compared to patients in the Control Group who received only dextrose dialysis solution (Table 6). There was also a marginal increase in lysine concentration (p=0.069). As in the previous study (Study No. DT88002) all but ornithine had been abnormally low before treatment, and these increases brought them closer to the normal range. Ornithine increased because it is a normal metabolite of arginine, which was present in Nutrineal™ PD2. Also, as was observed in the nitrogen balance study (Study No. DT88002), plasma taurine decreased during treatment with Nutrineal™ PD2.

Table 6 - Changes in Pre-exchange Plasma Amino Acid Concentrations in Controls and in Patients Treated with Nutrineal™ PD2 (Study No. RD-92-CA-042) (% Change at Three Months from Baseline)

Amino Acid	Controls (N=55)	Nutrineal™ PD2 (N=57)	p-value
Histidine	+ 3.7	+ 13.1	0.006
Threonine	+ 1.2	+ 22.4	0.004
Valine	- 0.2	+ 36.7	0.000
Ornithine	- 0.8	+ 14.0	0.006
Serine	+ 3.1	+ 16.2	0.003
Taurine	- 2.5	- 23.0	0.018

Since the peritoneal membrane is more permeable to large molecules than the synthetic or semi-synthetic membranes used in hemodialysis, losses of proteins and amino acids into peritoneal dialysate are significant. Various studies with amino acid dialysis solutions have shown conclusively that amino acids are efficiently absorbed from the peritoneal cavity. Since the fractional absorption is approximately 80% over 4 - 5 hours, one exchange with 2 L of a solution 1.0% or greater in amino acid content can easily replace the 3 - 4 g of amino acids and 8 - 10 g of proteins normally lost during peritoneal dialysis. Due to the loss of proteins during peritoneal dialysis, the protein requirement of an average sized Continuous Ambulatory Peritoneal Dialysis (CAPD) patient is increased by about 0.2 g protein per kg body weight per day. Peritonitis can transiently increase these peritoneal protein losses by 2-fold or more.

TOXICOLOGY

Human Studies

High-dose intravenous amino acid infusions were studied in humans and found to have no adverse reactions or gross abnormalities with respect to amino acid metabolism when single essential amino acids (tryptophan, leucine and methionine) were administered at up to 2.5 g/kg body weight in a 6 - 10 hour period[9].

Animal Studies

Acute Toxicity

Acute toxicity studies of highly purified amino acids were conducted as part of a 5-day subacute toxicity study in Sprague-Dawley rats. The data are summarized in Table 7 (see below). The

results showed that four of ten male rats injected intravenously at a dose of 120 mL/kg body weight and a rate of 4 mL/min of a 3% amino acid solution died immediately following the injection. There were no deaths in the female rats. Deaths were attributed to pulmonary hemorrhage resulting from the large injection volume. There was no local damage at the site of injection. The mechanism of toxicity was judged to be attributable to volume overload of the vascular system. Since the total blood volume of a rat is approximately 7% of body weight, infusion of 120 mL/kg at a rapid rate is equivalent to increasing the blood volume to 190 mL/kg from 70 mL/kg or 2.7-fold. The outcome of pulmonary hemorrhage and death is expected because of the limited capacity of the vascular system and rupture at the weakest vascular walls, the capillaries of the lung. This study shows the maximum non-lethal dose is greater than 80 mL/kg and the minimum lethal dose is less than 120 mL/kg.

The margin of safety is determined by comparing the no observed effect dose in the animal toxicity study with the clinical dose. The usual clinical dose of 1.1% amino acids is 5.24 mg/kg/min assuming 2 L of 11 g of amino acids/L given intraperitoneally to a 70 kg patient are absorbed in 60 min ([(11 g/L x 2 L) ÷ 70 kg] ÷ 60 min = 5.24 mg/kg/min). The maximum non-lethal dose in rats of 3% amino acids given a dose of 80 mL/kg at a rate of 4 mL/min and average body weight of 200 g is equivalent to a dose of 600 mg/kg/min. Thus the margin of safety is 600 mg/kg/min ÷ 5.24 mg/kg/min = 114. This margin of safety is an underestimate because the acute mechanism of toxicity, vascular hypervolemia, is not achievable by the intraperitoneal route of administration.

Table 7 - Intravenous Acute Toxicity of 3% Essential Amino Acids Solution

Species and Strain	Number of Animals & Sex/Group	Dosage* (mL/kg)	Number of Deaths
Rat, Sprague-Dawley	10 M + 10 F	40	none
Rat, Sprague-Dawley	6 M + 10 F	80	none
Rat, Sprague-Dawley	10 M + 10 F	120	4 M

Reference: Final Report, R.D. 01 - 101, CC1101B, Oct. 31, 1973

*3% essential amino acid solution was injected intravenously at a rate of 4 ml/min.

The acute toxicity of amino acids administered individually or in mixtures was studied in order to develop an amino acid solution suitable for parenteral injection in humans[10]. Male rats were given intraperitoneal injections of aqueous solutions or suspensions of crystalline amino acids. The dosages required for 50% lethality in rats range from 3 - 7g per kg body weight except for L-tryptophan, which has a LD_{50} of 1.6 g per kg body weight (see Table 8). Large dose increments which often approximated 50% of the LD_{50} were required for the LD_{99}. Symptoms of toxicity appeared from 10 minutes to 2 hours after the intraperitoneal injection; all amino acids caused dyspnea, hypothermia and extreme prostration. Body temperature was often reduced to 35°C before death. The prostration was usually associated with uncoordinated movements. Pathologic changes were most obvious in the kidney and liver. The glomeruli were congested and there were degenerative changes and vacuolization in renal tubular and hepatic parenchymal cells. The lesions were completely reversible if the animal survived.

Acute toxicity studies of mixtures of amino acids were also studied extensively[17]. The toxicity of mixtures of amino acids is not strictly additive and the LD_{50} of such mixtures is always less than would be calculated from the toxicities of each constituent single amino acid.

Table 8 - Intraperitoneal LD_{50} Doses of L-Amino Acids in Rats

Compound	LD_{50} mmoles/kg body weight*	LD_{50} mg/kg body/weight†,§
L-Alanine	37†	5078
L-Arginine HCl	18 ± 3	3793
L-Glycine	47†	3528
L-Histidine HCl	23 ± 3	3569
L-Isoleucine	52 ± 6	6821
L-Leucine	41 ± 9	5378
L-Lysine HCl	22 ± 4	4019
L-Methionine	29 ± 9	4328
L-Phenylalanine	32 ± 3	5286
L-Proline	no data	no data
L--Threonine	26 ± 2	3097
L-Tryptophan	8 ± 1	1634
L-Tyrosine	No data	no data
L-Valine	46 ± 7	5389

*Gullino, et al; 1956[10]
† Milne; 1968[11]
§ Lewis RJ, Tatken RL; 1982[12]

Repeat Dose Toxicity

The repeat-dose toxicity of Nutrineal™ PD2 and similar peritoneal dialysis and intravenous solutions was assessed in a series of studies including intraperitoneal administration and intravenous administration.

In a 28-day intraperitoneal study in rats (Baxter Study No. R062830524), groups of 10 animals received doses of a 1% or 2% purified amino acid solution (nearly twice that in the proposed drug product) with electrolytes (in a Dianeal® PD-2 formulation) at a dose of 30 mL/kg. The solution was administered intraperitoneally four times per day for a total daily dose of up to 120 mL/kg. A control group received a solution without amino acids or dextrose (e.g. sterile water plus electrolytes in a Dianeal® PD-2 formulation), and a reference group included a solution consisting of Dianeal® PD-2 with 4.25% dextrose. A fifth group received the 2% purified amino acid solution with electrolytes (in a Dianeal® PD-2 formulation) twice a day. The infused solutions were not drained as is the procedure in the clinical setting. No adverse toxicological findings were observed. A slightly higher spleen weight was seen in the animals treated with the solution with dextrose (reference group). Abdominal adhesions noted to some extent in all groups were attributed to the use of indwelling peritoneal catheters used to deliver the solutions. The dose of 120 mL/kg/day of 2% amino acid solution with electrolytes can be considered a no effect level. Noting that, in most cases, human exposure is one to two exchanges per day and that clinical usage involves removal of the solution after a prescribed dwell time, provides enhanced margins of safety.

In separate additional studies, amino acid solutions were also administered intravenously to rats for five or 30 days (Baxter Report Nos. R.D. 01-101,CC1101B, R.D. 1-101A,CC1101A). In the

five day study, doses of 40 mL/kg of a 3% essential amino acid solution resulted in no significant signs of toxicity or histopathological effects, and, despite a mild transient hypokinesia, this dosage was considered a no effect level. The highest dose in this study was initially 120 mL/kg, which resulted in mortality on the first day. A reduction in this dose to 80 mL/kg produced signs that were limited to hypokinesia that was more pronounced than that seen at the lower dose, but was nevertheless tolerated for the remaining four days. The dose of 80 mL/kg represents the average blood volume per kg of body weight in mammalian species, i.e. this dosage volume results in doubling the total vascular volume by the end of the infusion period.

In the 30-day intravenous study, rats received daily doses of 40 and 80 mL/kg of a 5% synthetic amino acid solution (SAAS). At 40 mL/kg, signs were limited to transient hyperkinesia and hyperpnea, with no significant signs of toxicity. This dose was considered a no effect level, since the observations were considered related to the volume of solution administered. At 80 mL/kg, effects included hyperemia, decrease in hemoglobin and hematocrit values, decreased serum calcium and uric acid values and increased serum sodium and potassium. One animal died following infusion. However, there were no histopathological changes noted in tissue evaluation.

Studies in dogs were carried out by the intravenous route of administration for five and 30 days (Baxter Report Nos. R.D. 1-101A, CC1101A, R.D. 1-101-3 (N255)). The five-day study involved the infusion of a solution of 5% synthetic amino acids (SAAS) plus 25% dextrose at 100 mL/kg/day (two different groups received 100 mL/kg/day at 7.5 and 3 mL/min) and 40 mL/kg of the same 5% synthetic amino acid solution plus 5% dextrose. At 40 mL/kg, there was no mortality. Clinical observations and increases in serum glucose, lactic acid and urea nitrogen and increases in urinary excretion were largely attributed to the volume and quantity of material administered. There were no histopathological changes in any tissue. However, the administration of 100 mL/kg resulted in mortality, and involved all dogs that received the solution at a rate of 7.5 mL/min and some dogs that received 3 mL/min. The cause of death was attributed to the rapid increase in blood osmolality consistent with an increase in plasma glucose. Lactic acid and urine nitrogen were also increased, as was urinary glucose. There were no effects discernible that would have been associated with the amino acids, although they could have contributed to the increased urea nitrogen levels due to the nitrogen content of amino acids.

In the 30-day study with dogs, a 5% synthetic amino acid solution (SAAS) was administered intravenously at 40 and 100 mL/kg five days per week. In this study, both of these doses were well tolerated; the only indication of a treatment related effect was an increase in serum urea nitrogen that was likely related to the administered nitrogen content associated with amino acid administration. There were no clinical, hematological, organ weight, body weight, or histopathological changes attributable to the administered amino acid solution.

Reproductive Toxicology

Reproduction and teratology studies have not been conducted with Nutrineal™ PD4. This is because the stress associated with an intraperitoneal route of administration would obscure appropriate scientific evaluation of these studies.

The effect of an oral diet of highly purified amino acids on growth, reproduction, embryotoxicity and lactation was studied in rats[13]. The purified amino acids were mixed with salts (minerals and electrolytes), vitamins (B and C), and glucose prepared in 50% aqueous solution and offered together with a separate supplement of fat-soluble vitamins in corn oil to weanling rats. At maturity, the animals were mated and produced normal litters with no evidence of reduced fertility or embryotoxicity. The F1 litters were maintained on the purified amino acid diets and, at maturity, yielded satisfactory litters (F2 generation) that were nursed to weaning. These studies indicate a purified amino acid diet, when supplemented with appropriate vitamins, salts, fat, and carbohydrate, does not have adverse effects on reproduction and fetal survival.

Genotoxicity Studies

The components in Nutrineal™ PD4 have been shown to be nonmutagenic considering that these components are food sources for all living organisms. All of the *in vitro* models for determining mutagenic potential utilize culture media composed of the same purified amino acids contained in this product. The amino acids contained in Nutrineal™ PD4 are highly purified, and meet the U.S. Pharmacopeial standards and are Generally Recognized as Safe (GRAS), as cited in US 21 CFR Parts 172 and 582. Hence, it is unlikely that the product is mutagenic.

Carcinogenicity Studies

Nutrineal™ PD4 has not been tested for carcinogenic potential in animal species because the route of administration is not practical for long-term application in laboratory animals. Oral feeding studies of purified diets with other nutrients have not shown evidence of carcinogenicity attributable to the amino acid content[13,14,15].

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PART III: CONSUMER INFORMATION

Nutrineal™ PD4
1.1% Amino Acid Peritoneal Dialysis Solution

This leaflet is Part III of a three-part "Product Monograph" published when Nutrineal™ PD4 was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Nutrineal™ PD4. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Nutrineal™ PD4 is a sterile peritoneal dialysis solution for the treatment of protein malnutrition. It does not contain glucose.

It is prescribed for you for your protein malnutrition and also have kidney failure which requires peritoneal dialysis. It may replace one (or two) of the dextrose-containing dialysis solutions during a one day period.

What it does:
Nutrineal™ PD4 contains amino acids that are absorbed into the blood during peritoneal dialysis and serve as building blocks from which the body can make protein.

Nutrineal™ PD4 draws fluid and wastes from your blood stream into your peritoneal cavity. This is the cavity in your abdomen (belly) between your skin and the peritoneum. The peritoneum is the membrane surrounding your internal organs such as your intestines and liver. The fluids and wastes are removed from your body when the Nutrineal™ PD4 solution is drained.

When it should not be used:
Do not use Nutrineal™ PD4:
- If you are allergic to any of the ingredients
- If your blood urea level is above 38 mmol/L
- If you have uremic symptoms such as loss of appetite, nausea or vomiting
- If you suffer from a disorder affecting amino acid metabolism
- If you suffer from liver insufficiency
- If your blood potassium level is too low
- If you have a disorder called metabolic acidosis
- If you have a surgically uncorrectable problem affecting your abdominal wall or cavity or uncorrectable problem that increases risk of abdominal infections
- If you have documented loss of peritoneal function due to severe peritoneal scarring

What the medicinal ingredients are:
Amino Acids:
Histidine
Isoleucine
Leucine
Lysine
Valine
Alanine
Arginine
Glycine
Methionine
Phenylalanine
Threonine
Tryptophan
Proline
Serine
Tyrosine

Electrolytes:
Calcium Chloride Dihydrate
Magnesium Chloride Hexahydrate
Sodium Chloride
Sodium Lactate

What the nonmedicinal ingredients are:
Hydrochloric acid (for pH adjustment)
Water for Injection

What dosage forms it comes in:
Nutrineal™ PD4 is a sterile solution available in TwinBag® containers in 2.0 L and 2.5 L sizes and Single Bag containers in 2.5 L size.

WARNINGS AND PRECAUTIONS

What you should tell your doctor before using Nutrineal™ PD4:
- If you have severe disorders affecting fat digestion
- If you have problems affecting your abdominal wall or cavity. For example if you have a hernia or an infection.
- If you had aortic graft placement.
- If you have severe lung disease (e.g. emphysema)
- If you have severe breathing difficulties
- If you use insulin or any other treatments for correcting hyperglycemia. Your doctor may need to adjust their dose.
- If you are undergoing treatment for secondary hyperparathyroidism, your doctor will decide if you can use a dialysis solution with a low calcium content.
- If you are pregnant or breastfeeding. Nutrineal™ PD4 is not recommended during pregnancy or while breast-feeding unless your doctor advises differently.

Tell your doctor immediately if the following occurs while taking Nutrineal™ PD4:
- If you experience loss of appetite, nausea or vomiting. Your doctor may need to reduce the number of Nutrineal™ PD4 exchanges or stop Nutrineal™ PD4 treatment.
- If you experience abdominal pain or notice cloudiness, haziness or particles in the drained fluid. This may be a sign of peritonitis (inflamed peritoneum) or infection. You should contact your medical team urgently. Note the batch number and bring it along with the drained fluid bag to your medical team. They will decide if the treatment should be stopped or any corrective treatment started. For example if you have an infection your doctor may perform some tests to find out which antibiotic will be best for you. Until your doctor knows which infection you have, he may give you an antibiotic that is effective against a wide number of different bacteria. This is called a broadspectrum antibiotic.
- If any signs or symptoms of an allergic reaction develop,

intraperitoneal administration of Nutrineal™ PD4 must be stopped immediately. Your doctor might need to treat your allergy immediately.

Other Warnings:

- During peritoneal dialysis your body may lose protein, amino acids and vitamins. Your doctor will know if these need to be replaced.
- A rare complication of peritoneal dialysis called encapsulating peritoneal sclerosis (EPS), may occur after being treated with perioneal dialysis for an extended period of time. Symptoms and signs are usually nonspecific, but may include severe abdominal pain, inability to remove fluid, persistent nausea and vomiting and intestinal blockage. Diagnosis is confirmed by your doctor.
- Your doctor should check your potassium levels regularly. If they fall too low your doctor may give you some potassiumto compensate.
- Your doctor should advise you about particular precautions as they apply to you. Your doctor should monitor your blood parameters at regular intervals and ensure that they are adequate during your treatment.
- Together with your doctor, keep a record of your dietary protein intake, your fluid balance and your body weight.

INTERACTIONS WITH THIS MEDICATION

- Tell your doctor if you are taking or have recently taken any other medications, including medications obtained without a prescription. If you use other medications, your doctor may need to increase their dose. This is because peritoneal dialysis treatment increases the elimination of certain medications.
- Be cautious if you use heart medications known as cardiac glycosides (e.g. digoxin). Your heart medications may not be as effective or its toxicity may be increased. You may:
  - need potassium and calcium supplements
  - develop an irregular heartbeat (an arrhythmia)

Your doctor should monitor you closely during treatment, especially your potassium levels.

PROPER USE OF THIS MEDICATION

Usual Adult dose:

Your doctor should prescribe you the appropriate number of bags you must use. Usually, it varies from one bag of 2.0 litres to one bag of 2.5 litres every day.
If you are below 18 years of age, your doctor should assess carefully the prescription of Nutrineal™ PD4.
Your doctor should re-evaluate your treatment after 3 months if there is no improvement in your nutritional status.

Aministration Instructions:

- To do your Nutrineal™ PD4 exchange, it is very important that you follow the steps shown to you in your training. All surfaces and connecting parts must be clean to avoid serious infection. If you need more help or have any questions, you should contact your doctor.
- Before use, warm the bag to 37°C. Use only dry heat (for example, a heating pad or warming plate). Never immerse in water to warm the bag. Never use a microwave oven to warm the bag.
- Use only if the solution is clear and the container undamaged.
- Use aseptic technique throughout the administration of the solution. Aseptic technique is the effort taken to keep yourself from micro-organisms infection.
- Use each bag only once.
- Discard any unused remaining solution.

Preparation and Administration for the Single Bag Container:
Follow the instructions in user manual or directions accompanying tubing sets and devices for automated peritoneal dialysis.

Preparation and Administration for the TWIN BAG® Container:

1. Do not remove from the carton until ready for use.
2. Remove container from overpouch.
3. Inspect solution container and frangible to ensure that there are no leaks, and the solution has not expired. If leaks are detected, or the expiration date has lapsed, discard container.
4. Inspect the patient connector to ensure the pull ring is attached. Do not use if pull ring is not attached to the connector.
5. Inspect tubing and drainage container for presence of solution. If solution is noted, discard unit. NOTE: Small water droplets are acceptable.
6. Ensure patient transfer set is closed.
7. Break frangible at patient connector.
8. Remove pull ring from the patient connector.
9. Remove disconnect cap from patient transfer set. Immediately attach patient transfer set connector to the patient connector by twisting the connector until firmly secured.
10. Clamp new bag solution line.
11. Break frangible at container port.
12. Hang the new solution container.
13. Place the drainage container below the level of the peritoneum.

Proceed with either Procedure A or Optional: Procedure B

Procedure A

14. Open transfer set clamp to drain solution from the peritoneal cavity.
15. Close transfer set line clamp after drainage is complete.
16. Open new solution line clamp and allow the new solution to flow into the drainage container for five seconds.
17. Clamp drain line.
18. Open transfer set clamp and allow the solution to flow into the peritoneal cavity.
19. Close transfer set clamp when infusion is complete.
20. Open a new disconnect cap following the directions accompanying the cap.

21. Disconnect the patient transfer set from the TWIN BAG® set and attach the new disconnect cap to the transfer set.

Optional: Procedure B

14. Open new solution line clamp and allow the new solution to flow into the drainage container for five seconds.
15. Clamp new solution line.
16. Open transfer set clamp to drain solution from the peritoneal cavity.
17. Clamp drain line.
18. Open new solution line and allow solution to flow into the peritoneal cavity.
19. Close transfer set clamp when infusion is complete.
20. Open a new disconnect cap following the directions accompanying the cap.
21. Disconnect the patient transfer set from the TWIN BAG® set and attach the new disconnect cap to the transfer set.

- Nutrineal™ PD4 should be infused based on your need for adequate dialysis, as determined by your doctor. When draining the fluid after the dwell, always check your drained fluid for cloudiness or fibrin. Fibrin looks like clumps or stringy material in the drained solution. Cloudy drained fluid or fibrin may mean you have an infection. Call your doctor if your drained fluid is cloudy or contains fibrin.
- If you infuse too much NUTRINEAL you may get:
  - abdominal distension
  - a feeling of fullness

  Contact your doctor immediately. He will advise what to do.

Overdose:
Overdose may result in fluid overload and/or electrolyte imbalances.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, Nutrineal™ PD4 may cause side effects. Side effects may inlcude feeling of weakness, headache, fever, malaise and asthenia.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical help
		Only if severe	In all cases	
Very Common	• Nausea / vomiting, anorexia, nausea, abdominal pain (symptoms for gastrointestinal disorders)	✓		
	• Body swelling (symptoms for increase in body fluid volume)		✓	
Common	• Gastritis		✓	
	• Shortness of breath		✓	
	• Dizziness, drop in blood pressure (symptoms for decrease in body fluid volume)		✓	
	• Anemia (symptoms like weakness, or fatigue, general malaise and sometimes poor concentration)		✓	
	• Depression		✓	
	• Redness, swelling, soreness around catheter site (symptoms for catheter site infection)		✓	
Unknown	• Allergic reactions (symptoms like lumpy skin rash or hives anywhere, angioedema, pruritus on the body)			✓
	• Abdominal discomfort, peritoneal cloudy effluent, fever (symptoms for inflammation of the peritoneum)		✓	

HOW TO STORE IT

Protect from light until ready to use. Store at 15-25°C. Protect Nutrineal™ PD4 from freezing. Do not remove from the carton until ready for use. Any unused portion of the solution should be discarded.

Keep out of sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.baxter.ca
or by contacting the sponsor, Baxter Corporation, at:
1-800-387-8399

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