1.3.1.1. PACKAGE INSERT

SCHEDULING STATUS: **S3**

PROPRIETARY NAME **EXTRANEAL®**

(and dosage form): **(Peritoneal Dialysis Solution)**

COMPOSITION:

Each 1 litre of **EXTRANEAL** contains:

Icodextrin	75 g
Sodium Chloride	5,4 g
Sodium Lactate	4,5 g
Calcium Chloride	0,257 g
Magnesium Chloride	0,051 g

Theoretical osmolarity: 284 (milliosmoles per litre).

Theoretical osmolality: 301 (milliosmoles per kg).

Electrolyte solution content per 1 000 ml:

Sodium	133 mmol
Calcium	1,75 mmol
Magnesium	0,25 mmol
Chloride	96 mmol
Lactate	40 mmol

PHARMACOLOGICAL CLASSIFICATION:

A.34 (Other)

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties

Icodextrin is a starch-derived glucose polymer which acts as an osmotic agent when administered intraperitoneally for continuous ambulatory peritoneal dialysis (CAPD). A 7,5 % solution is approximately iso-osmolar to serum but produces sustained ultrafiltration over a period up to 12 hours in CAPD. There is a reduction in calorie load compared to hyperosmolar glucose solutions.

The volume of ultrafiltrate produced is comparable to that with 4,25 % glucose monohydrate when used in CAPD. Blood glucose and insulin levels remain unaffected.

Ultrafiltration is maintained during episodes of peritonitis.

The recommended dosage is limited to a single exchange in each 24 hour period, as part of a CAPD or automated peritoneal dialysis (APD) regimen.

Pharmacokinetic Properties

Carbohydrate polymer levels in blood reach steady state after about 7 – 10 days when used on a daily basis for overnight dialysis. The polymer is hydrolysed by amylase to smaller fragments which are cleared by peritoneal dialysis. Steady state plasma levels of 1,8 mg/ ml have been measured for oligomers of glucose units greater than 9 (G9) and there is a rise in serum maltose (G2) to 1,1 mg/ ml but there is no significant change in serum osmolality. When used for the long day time dwell in APD, maltose levels of 1,4 mg/ ml have been measured but with no significant change in serum osmolality. The long term effects of raised plasma levels of maltose and glucose polymer are unknown, but there is no reason to suppose these to be harmful.

INDICATIONS:

EXTRANEAL is recommended as a once daily replacement for a single glucose exchange for 6 – 12 hours duration as part of a CAPD or APD regimen for the treatment of chronic renal failure. It may be used for patients in whom efficacy of ultrafiltration on glucose solutions is no longer effective.

CONTRA-INDICATIONS:

EXTRANEAL should not be used in pregnancy and lactation, (See Pregnancy and Lactation), children and patients with a known allergy to starch based polymers and/or icodextrin and in patients with maltose or isomaltose intolerance or patients with glycogen storage disease.

EXTRANEAL is also contra-indicated in patients with a history of abdominal surgery in the month preceding commencement of therapy or in patients with abdominal fistulae, tumours, open wounds, herniae or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity.

Acute renal failure.

Icodextrin should not be used in patients with conditions which preclude normal nutrition, with impaired respiratory function or with potassium deficiency.

EXTRANEAL is contra-indicated in patients with pre-existing lactic acidosis.

WARNINGS AND SPECIAL PRECAUTIONS:

Women of childbearing potential should be treated with **EXTRANEAL** only when adequate contraceptive precautions have been taken.

In diabetic patients, blood glucose levels should be regularly monitored, and the dosage of insulin or other treatment for hyperglycaemia should be adjusted following initiation of treatment with **EXTRANEAL.**

Patients with diabetes mellitus often need additional insulin in order to maintain glycaemic control during Peritoneal Dialysis (PD). Transfer from glucose based PD solution to **EXTRANEAL** may necessitate an adjustment of the usual insulin dosage.

Insulin can be administered intraperitoneally. Blood glucose measurement must be done with a glucose specific method to prevent maltose interference. **Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) or glucose-dye-oxidoreductase-based methods should not be used. Also, the use of some glucose monitors and test strips using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD) methodology has resulted in falsely elevated glucose readings due to the presence of maltose. The manufacturer(s) of the monitor**

and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose results.

If GDH-PQQ or glucose-dye-oxidoreductase (GDO) or GDH-FAD -based methods are used, using EXTRANEAL may cause a falsely high glucose reading, which could result in the administration of more insulin than needed.
Administration of more insulin than needed has caused hypoglycaemia, which can result in loss of consciousness, coma, neurological damage and death. Additionally, falsely elevated blood glucose measurements due to maltose interference may mask true hypoglycaemia and allow it to go untreated with similar consequences.

Falsely elevated glucose levels may be measured up to two weeks following cessation of EXTRANEAL (icodextrin) therapy when GDH-PQQ or GDO-based blood glucose monitors and test strips are used.
Because GDH-PQQ, GDO or GDH-FAD-based blood glucose monitors may be used in hospital settings, it is important that the health care providers of peritoneal dialysis patients using EXTRANEAL (icodextrin) carefully review the product information of the blood glucose testing system, including that of test strips, to determine if the system is appropriate for use with EXTRANEAL (icodextrin). See interactions.
To avoid improper insulin administration, educate patients to alert health care providers of this Interaction whenever they are admitted to the hospital.

A decrease in serum amylase levels has also been noticed as a common finding in PD patients on long term treatment. The decrease has not been reported to be accompanied with any side effects. However, it is not known whether subnormal amylase levels may mask the rise in serum amylase, commonly seen during acute pancreatitis. An increase in serum alkaline phosphatase of approximately 20 IU/L was seen during clinical trials. There were individual cases where increased alkaline phosphatase was associated with elevated SGOT/ AST levels.
Treatment should be initiated under the supervision of a medical practitioner.

Peritoneal reactions, including abdominal pain, cloudy effluents with or without bacteria (aseptic peritonitis) have been associated with **EXTRANEAL**. In case of peritoneal reactions, the patient should keep the icodextrin drained fluid bag along with the batch number, and the applicant or medical representative should be contacted for analysis of the drained fluid bag.
The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of infection or aseptic peritonitis. Patients should be asked to inform their physician if this occurs and appropriate microbiological samples should be drawn. The initiation of antibiotic treatment should be a clinical decision based on whether or not infection is suspected. If other possible reasons for cloudy fluid have been excluded, **EXTRANEAL** should be stopped and the result of this action evaluated. If **EXTRANEAL** is stopped and the fluid becomes clear afterwards, **EXTRANEAL** should not be reintroduced unless under close supervision. If by re-challenging with **EXTRANEAL**, the cloudy fluid recurs then this patient should not be prescribed **EXTRANEAL** again. Alternative peritoneal dialysis therapy should be initiated and the patient should be kept under close supervision.

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 **EXTRANEAL**. Fatal outcomes of EPS have been reported with **EXTRANEAL**.

Patients with severe lactic acidosis should not be treated with **EXTRANEAL** (See Contra-Indications). It is recommended that patients with conditions known to increase the risk of lactic acidosis [e.g., acute renal failure, inborn errors of metabolism, treatment with medicines such as metformin and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)] must be monitored for occurrence of lactic acidosis before the start of treatment and during treatment with lactate-based peritoneal dialysis solutions.

When prescribing the solution to be used for an individual patient, consideration should be given to the potential interaction between the dialysis treatment and therapy directed at other existing illnesses. Serum potassium levels should be monitored carefully in patients treated with cardiac glycosides.

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.

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.

Overinfusion of an **EXTRANEAL** volume into the peritoneal cavity may be characterized by abdominal distension, feeling of fullness and/or shortness of breath. Treatment of **EXTRANEAL** overinfusion is to drain the **EXTRANEAL** from the peritoneal cavity.

Potassium is omitted from **EXTRANEAL** 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 mmol/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 medical practitioner.

Fluid, hematology, blood chemistry, and electrolyte concentrations should be monitored periodically, including, magnesium and bicarbonate. If serum magnesium levels are low, oral magnesium supplements or peritoneal dialysis solutions containing higher magnesium concentrations may be used.

Decreases in serum sodium and chloride have been observed in patients using **EXTRANEAL**.

Rarely, serious hypersensitivity reactions to **EXTRANEAL** have been reported such as toxic epidermal necrolysis, angioedema, serum sickness, erythema multiforme and leukocystoclastic vasculitis. If a serious reaction is suspected, discontinue **EXTRANEAL** and institute appropriate treatment as clinically indicated.

Effects on ability to drive and operate machines

- Treatment with **EXTRANEA**L may cause fatigue, weakness, blurred vision or dizziness.
- Ability to drive and operate machines is affected when in treatment with **EXTRANEAL**.

INTERACTIONS:

The blood concentrations of dialysable drugs may be reduced by dialysis. Corrective therapy should be instituted if necessary. In patients using cardiac glycosides, plasma levels of potassium and calcium must be carefully checked. In the event of abnormal levels, appropriate actions should be taken.

Drug-Laboratory Test Interferences

Blood glucose measurement must be done with a glucose specific method to prevent maltose interference. Only use glucose monitors and test strips that utilise glucose oxidase or hexokinase methods. Glucose dehydrogenase pyrrolquinolinequinone (GDH PQQ) or glucose-dye-oxidoreductase -based methods should not be used.

It is recommended that reference is made to the relevant section of the glucose test kit product leaflet to ascertain that interference while using icodextrin-based dialysis therapy is not described. (See Warnings)

An apparent decrease in serum amylase activity has been observed in patients administered **EXTRANEAL** (See Warnings).

Incompatibilities

- Consult with pharmacist familiar with peritoneal dialysis, if available. If, in the informed judgment of the medical practitioner, it is deemed advisable to introduce additives, use aseptic technique.
- Refer to directions for use of accompanying medicines to obtain full information on additives.
- Some medicine additives may be incompatible with **EXTRANEAL**.
    - Addition of Potassium

      Potassium is omitted from **EXTRANEAL** solutions because dialysis may be performed to correct hyperkalaemia. In situations where there is a normal serum potassium level or hypokalaemia, the addition of potassium chloride (up to a concentration of 4 mmol/L) may be indicated to prevent severe hypokalaemia. The decision to add potassium chloride should be made by the medical practitioner after careful evaluation of serum potassium.
    - Addition of Heparin

      No interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with **EXTRANEAL**.
    - Addition of Antibiotics

      No formal clinical interaction studies have been performed. In vitro compatibility studies with **EXTRANEAL** and the following antibiotics have demonstrated no effects with regard to minimum inhibitory concentration (MIC): vancomycin, cefazolin, ampicillin, ampicillin/flucoxacillin, ceftazidime, gentamicin, and amphotericin. However, aminoglycosides should not be mixed with penicillins due to chemical incompatibility.

PREGNANCY AND LACTATION:

EXTRANEAL should not be used during pregnancy or while breastfeeding.

Women of childbearing potential should be treated with **EXTRANEAL** only when adequate contraceptive precautions have been taken.

DOSAGE AND DIRECTIONS FOR USE:

For intraperitoneal administration only. Not for intravenous administration.

EXTRANEAL is recommended for use during the longest dwell period, i.e. in CAPD usually overnight and in APD for the long daytime dwell.

Adults: By intraperitoneal administration limited to a single exchange in each 24 hour period, as part of a CAPD or APD regimen.

Elderly: As for Adults.

Children: Not recommended for use in children (less than 18 years).

The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be initiated and supervised by the medical practitioner.

The volume to be instilled should be given over a period of approximately 10 to 20 minutes at a rate which the patient finds comfortable. For adult patients of normal body size the instilled volume should not exceed 2,0 L.

For larger patients (more than 70 – 75 kg), a fill volume of 2,5 L may be used.

If the instilled volume causes discomfort due to abdominal tension the instilled volume should be reduced. The recommended dwell time is between 6 and 12 hours in CAPD and 14 – 16 hours in APD. Drainage of the fluid is by gravity at a rate comfortable for the patient. The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of infection or aseptic peritonitis.

Do not administer unless the solution is clear and the container undamaged.

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

Aseptic technique should be observed throughout the procedure.

To reduce discomfort on administration, the solution may be warmed in the oversealed bag to a temperature of 37 °C prior to use.

This should be done using dry heat, ideally using a warming plate specially designed for the purpose. The bag should not be immersed in water to warm it, to avoid contamination of connectors. It should also not be heated in a microwave oven due to the potential for patient injury or discomfort.

Compatibility with additives must be checked before admixture. In addition, the pH and salts of the solution must be taken into account.

Diabetic patients should only use glucose monitors and test strips that utilise glucose oxidase or hexokinase methods.

A range of antibiotics including vancomycin, cefazolin, ampicillin/flucloxacillin, ceftazidime, gentamycin, amphotericin and insulin have shown no evidence of incompatibility with **EXTRANEAL**.

The product should be used immediately after any medicine addition.

Discard any unused remaining solution.

For single use only.

SIDE-EFFECTS:

Frequency has been evaluated using the following criteria: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

†This table represents an integration of safety data from clinical trials involving 493 patients:

Side-Effects from Clinical Trials

Clinical Trial Adverse Reactions†			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency***	**Frequency Percentage or Ratio N=493**
INFECTIONS AND INFESTATIONS	Influenza Furuncle Infection	Uncommon Uncommon Uncommon	0,6 0,2 0,2

Clinical Trial Adverse Reactions[†]			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency***	**Frequency Percentage or Ratio N=493**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anaemia	Uncommon	0,4
	Leukocytosis	Uncommon	0,6
	Eosinophilia	Uncommon	0,2
ENDOCRINE DISORDERS	Parathyroid disorder	-**	-**
METABOLISM AND NUTRITION DISORDERS	Dehydration	Common	2,0
	Hypovolaemia	Common	1,0
	Hypoglycaemia	Uncommon	0,4
	Hyponatraemia	Uncommon	0,4
	Hyperglycaemia	Uncommon	0,2
	Hypervolaemia	Uncommon	0,8
	Anorexia	Uncommon	0,8
	Hypochloraemia	Uncommon	0,8
	Hypomagnesaemia	Uncommon	0,4
	Hypoproteinaemia	Uncommon	0,4
PSYCHIATRIC DISORDERS	Thinking abnormal	Uncommon	0,2
	Anxiety	Uncommon	0,2
	Nervousness	Uncommon	0,2
NERVOUS SYSTEM DISORDERS	Dizziness	Common	1,8
	Headache	Common	1,4
	Hyperkinesia	Uncommon	0,2
	Paraesthesia	Uncommon	0,6
	Ageusia	Uncommon	0,2
EAR AND LABYRINTH DISORDERS	Tinnitus	Common	3,6

Clinical Trial Adverse Reactions[†]			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency***	**Frequency Percentage or Ratio N=493**
CARDIAC DISORDERS	Cardiovascular disorder	Uncommon	0,2
	Tachycardia	Uncommon	0,2
VASCULAR DISORDERS	Hypotension	Common	3,2
	Hypertension	Common	2,6
	Orthostatic hypotension	Uncommon	0,2
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Pulmonary oedema	Uncommon	0,2
	Dyspnoea	Uncommon	0,4
	Cough	Uncommon	0,2
	Hiccups	Uncommon	0,2
	Lung disorder	Uncommon	0,4
GASTROINTESTINAL DISORDERS	Abdominal pain	Common	1,6
	Abdominal distension	-**	-**
	Intestinal obstruction	Uncommon	0,2
	Peritonitis	Uncommon	0,6
	Bloody peritoneal effluent	Uncommon	0,2
	Diarrhoea	Uncommon	0,6
	Gastric ulcer	Uncommon	0,2
	Gastritis	Uncommon	0,2
	Gastrointestinaldisorder	Uncommon	0,4
	Vomiting	Uncommon	0,2
	Constipation	Uncommon	0,4
	Dyspepsia	Uncommon	0,6
	Nausea	Uncommon	0,2
	Dry mouth	Uncommon	0,4
	Flatulence	Uncommon	0,2

Clinical Trial Adverse Reactions[†]			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency***	**Frequency Percentage or Ratio N=493**
SKIN AND SUBCUTANEOUS DISORDERS	Dermatitis exfoliative	Common	1,6
	Rash	Common	5,5
	Pruritus	Common	1,4
	Urticaria	Uncommon	0,2
	Dermatitis bullous	Uncommon	0,2
	Psoriasis	Uncommon	0,4
	Rash, maculo-papular	Uncommon	0,2
	Skin ulcer	Uncommon	0,2
	Eczema	Uncommon	0,2
	Nail disorder	Uncommon	0,6
	Skin disorder	Uncommon	0,2
	Dry skin	Uncommon	0,2
	Skin discolouration	Uncommon	0,2
MUSCULOSKELETAL, CONNECTIVE TISSUE DISORDERS	Bone pain	Uncommon	0,1
	Muscle spasms	Uncommon	0,4
	Myalgia	Uncommon	0,4
	Neck pain	Uncommon	0,4
RENAL AND URINARY DISORDERS	Renal pain	Uncommon	0,2

Clinical Trial Adverse Reactions[†]			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency***	**Frequency Percentage or Ratio N=493**
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	Peripheral Oedema	Common	1,4
	Asthenia	Common	1,2
	Chest pain	Uncommon	0,4
	Catheter-related complication	Uncommon	0,2
	Face oedema	Uncommon	0,2
	Oedema	Uncommon	0,.6
	Pain	Uncommon	0,2
INVESTIGATIONS	Decreased urine output	-**	-**
	Laboratory test abnormal	Common	2,6
	Increased alanine aminotransferase	Uncommon	0,4
	Increased aspartate aminotransferase	Uncommon	0,4
	Increased blood alkaline phosphatase	Uncommon	0,6
	Abnormal liver function test	Uncommon	0,6
	Decreased weight	Uncommon	0,2
	Increased weight	Uncommon	0,6
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	Injury	Uncommon	0,2

Post-Marketing Side Effects

In addition to the side-effects noted in clinical trials, the following side-effects have been reported in the post-marketing experience.

Infections and infestations: Fungal peritonitis, Peritonitis bacterial, Catheter site infection, Catheter related infection.

Blood and lymphatic system disorders: Thrombocytopenia, Leukopenia.

Immune system disorders: Serum sickness, Hypersensitivity, Leukocytoclastic vasculitis.

Metabolism and nutrition disorders: Shock hypoglycaemia, Fluid overload, Fluid imbalance.

Nervous system disorders: Hypoglycaemic coma, Burning sensation.

Eye disorders: Vision blurred.

Respiratory, thoracic, and mediastinal disorders: Bronchospasm, Stridor.

Gastrointestinal disorders: Sclerosing encapsulating peritonitis, Aseptic peritonitis, Peritoneal cloudy effluent, Ileus, Ascites, Inguinal hernia, Abdominal discomfort.

Skin and subcutaneous disorders: Toxic epidermal necrolysis, Erythema multiforme, Angioedema, Urticaria generalized, Toxic skin eruption, Swelling face, Periorbital oedema, Exfoliative rash, Skin exfoliation, Prurigo, Rash (including macular, papular, erythematous), Dermatitis (including allergic and contact), Drug eruption, Erythema, Onychomadesis, Skin chapped, Blister.

Musculoskeletal, connective tissue disorders: Arthralgia, Back pain, Musculoskeletal pain.

Reproductive system and breast disorders: Penile oedema, Scrotal oedema.

General disorders and administration site conditions: Discomfort, Pyrexia, Chills, Malaise, Drug effect decreased, Drug ineffective, Catheter site erythema, Catheter site inflammation, Infusion related reaction (including Infusion site pain, Instillation site pain).

Injury, poisoning and procedural complications: Device interaction

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No data is available on the effects of overdosage. However, continuous administration of more than one bag of **EXTRANEAL** in 24 hours would increase plasma levels of carbohydrate metabolites and maltose. The effects of such an increase are unknown but an increase in plasma osmolality may occur. Treatment could be managed by icodextrin-free peritoneal dialysis or haemodialysis.

IDENTIFICATION:

A clear, colourless to pale yellow solution, practically free of visible particles.

PRESENTATION:

EXTRANEAL peritoneal dialysis solution in Viaflex® plastic containers in the Twin-bag and Single-bag configuration is available in the following container sizes with fill volumes as indicated below.

Fill Volume	Container Size
1 500 ml	2 L
2 000 ml	2 L/3 L
2 500 ml	3 L

STORAGE INSTRUCTIONS:

EXTRANEAL has a shelf-life of 2 years. Do not use the product after the expiry date shown on the carton and product label.

Store at a temperature between 4 °C - 30 °C. Do not use unless the solution is clear and the container is undamaged. Any unused portion of dialysis solution in a bag should be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

38/34/0172

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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