

**PACKAGE INSERT**SCHEDULING STATUS: **S1**

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.

*MA* 19/11/2007

**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 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.

In common with other peritoneal dialysis fluids, icodextrin should not be used in patients with conditions which preclude normal nutrition, with impaired respiratory function or with potassium deficiency.

**WARNINGS:**

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

Patients should be carefully monitored to avoid over or under hydration. Enhanced ultrafiltration, particularly in elderly patients, may lead to dehydration, resulting in hypotension and possibly neurological symptoms.

An accurate fluid balance record should be kept and the patient's body weight monitored.

Blood chemistry, haematology and plasma osmolality should be monitored at regular intervals.

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

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. If GDH-PQQ or glucose-dye-oxidoreductase -based methods are used, using EXTRANEAL may cause a falsely high glucose reading, which could result in the administration of more insulin than needed. This can cause 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.**

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 Interactions).

A decrease in the serum sodium and chloride level has been observed in some patients. Though these decreases have been regarded as clinically non-significant, it is recommended that serum electrolyte levels are monitored regularly.

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 physician.

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

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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.

### **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. 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. (e.g, SureStep® Pro and SureStep® Flexx monitors). 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)

### **Incompatibilities**

A range of antibiotics including vancomycin, cefazolin, ampicillin/flucloxacillin, ceftazidime, gentamycin, amphotericin and insulin have shown no evidence of incompatibility with **EXTRANEAL**. In addition, the pH and salts of the solution must be taken into account.

### **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.

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**DOSAGE AND DIRECTIONS FOR USE:**

For intraperitoneal administration only.

**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 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.

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.

Drug compatibility 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 & test strips that utilise glucose oxidase or hexokinase methods (e.g , SureStep ® Pro and SureStep ® Flexx monitors)

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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 drug addition.

Discard any unused remaining solution.

For single use only.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**

Undesirable effects which occurred in patients treated with **EXTRANEAL** from the clinical trials are listed below.

	Adverse Drug Reaction	Frequency*
<b>General disorders</b>	Abdominal pain	Common
	Asthenia	Common
	Headache	Common
	Abnormal laboratory tests (increased alkaline phosphatase, AST/ALT (< 1%), decreased serum amylase and decreased sodium and chloride levels)	Common
<b>Vascular disorders</b>	Hypertension	Common
	Hypotension	Common
<b>Metabolism and Nutrition disorders</b>	Hypovolaemia and dehydration	Common
	Oedema	Common
<b>Nervous System disorders</b>	Dizziness	Common
<b>Skin and Subcutaneous tissue disorders</b>	Rash	Common
	Pruritus	Common
	Exfoliation	Common

\* The term common means a frequency between 1 and 10%.

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Some undesirable effects, probably related to **EXTRANEAL**, are indicated below. The frequency is not known.

#### **Skin and Subcutaneous tissue disorders**

**EXTRANEAL** associated skin reactions, including rash and pruritus, are generally mild or moderate in severity. Occasionally, these rashes have been associated with exfoliation. In the event of this occurring and depending on the severity, **EXTRANEAL** should be withdrawn at least temporarily.

#### **General disorders**

Enhanced ultrafiltration, particularly in the elderly patients, may lead to dehydration, resulting in hypotension, dizziness and possibly neurological symptoms.

#### **Metabolism and Nutrition disorders**

Hypoglycaemic episodes in diabetic patients.  
Increase in serum alkaline phosphatases.

#### **Gastrointestinal disorders**

Peritoneal reactions, including abdominal pain, cloudy effluents with or without bacteria and aseptic peritonitis. (Refer to "WARNINGS")

Other undesirable effects of peritoneal dialysis related to the procedure.

The following undesirable effects are often reported:

#### **General disorders and Administration Site conditions**

- Those which are related to the procedure, include peritonitis (septic or aseptic) with or without abdominal pain, cloudy effluent and sometimes fever, bleeding, catheter blockage, infection around the catheter (signs of inflammation: redness and secretion), hypervolaemia, hypovolaemia,

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hypertension, hypotension, dehydration, oedema, constipation, hernia of the abdominal cavity, ileus, loss of appetite, dyspepsia, nausea and vomiting, dizziness, fatigue, headache, shoulder pain, pruritus and abnormal laboratory tests results.

- Those which are generally related to peritoneal dialysis solutions such as **EXTRANEAL**, are seen less frequently than those related to the procedure and include:

**Gastrointestinal disorders**

Cloudy effluent/aseptic peritonitis.

**Metabolism and Nutrition disorders**

Electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia and hypercalcaemia).

**Vascular disorders**

Fainting.

**Musculoskeletal and Connective tissue disorders**

Muscle cramping.

**Respiratory, thoracic and mediastinal disorders**

Respiratory symptoms associated with shortness of breath and weakness.

**Special Precautions**

Please refer to "WARNINGS".

**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.

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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.

<u>Fill Volume</u>	<u>Container Size</u>
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

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

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Johannesburg

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