

**Blood glucose measurement with EXTRANEAL must be done with a glucose-specific method to avoid interference resulting in unrecognised hypoglycemia. If non-specific glucose test methods (GDH-PQQ or Glucose-dye-oxidoreductase) are used, loss of consciousness, neurological damage or death may occur.**

**(i) Name of drug:**

EXTRANEAL (Icodextrin 7.5%) Peritoneal Dialysis Fluid

**(ii) Description:**

EXTRANEAL is a sterile peritoneal dialysis fluid containing Icodextrin as the active ingredient at a concentration of 7.5% w/v in an electrolyte solution. It is presented in a flexible PVC bag and is sterile, non-pyrogenic and contains no bacteriostatic or antimicrobial agents or added buffers.

Each 1000mL of EXTRANEAL contains:

Icodextrin	75 g
Sodium Chloride	5.4g
Sodium Lactate	4.5g
Calcium Chloride	257mg
Magnesium Chloride	51mg
Sodium Hydroxide	pH adjustment
Hydrochloric acid	pH adjustment
Water for injections	q.s.

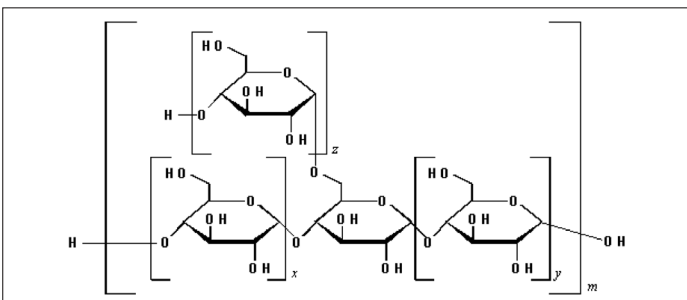
Theoretical Osmolarity 284 (milliosmoles per litre)

Electrolyte Solution Content per 1000mL:

Sodium	133 mmol
Calcium	1.75 mmol
Magnesium	0.25 mmol
Chloride	96 mmol
Lactate	40 mmol

Icodextrin is an  $\alpha$  (1-4) linked glucose polymer that contains 5-10%  $\alpha$  (1-6) links. It is produced by the hydrolysis of starch and fractionated by membrane separation technology to produce material with the desired molecular weight distribution (85% w/w within the molecular weight range 1,640-45,000).

The CAS Registration Number for icodextrin is 337376-15-5. Its chemical structure is shown below: -



**(iii) Pharmacology:**

**Pharmacodynamic Properties:** Icodextrin is a starch derived glucose polymer that acts as an osmotic agent when administered intraperitoneally for continuous ambulatory peritoneal dialysis. A 7.5% solution is approximately iso-osmolar to serum but produces sustained ultrafiltration over a period up to 12 hours in Continuous Ambulatory Peritoneal Dialysis (CAPD). The volume of ultrafiltrate produced is comparable to that with 3.86% glucose when used in CAPD. Blood glucose and insulin levels remain unaffected.

**Pharmacokinetic Properties:** In a single-dose pharmacokinetic study using EXTRANEAL (n=13), a median of 40% (60 g) of the

instilled icodextrin was absorbed from the peritoneal solution during a 12-hour dwell. Plasma levels of icodextrin rose during the dwell and declined after the dwell was drained. Peak plasma levels of icodextrin plus its metabolites (median  $C_{peak}$  2.2g/L) were observed at the end of the long dwell exchange (median  $T_{max}$  = 13 hours). Plasma levels return to baseline values within 7 days following cessation of icodextrin administration.

At steady-state, the mean plasma level of icodextrin plus its metabolites was about 5 g/L. In multidose studies, steady-state levels of icodextrin were achieved within one week.

Icodextrin is metabolised by alpha-amylase into oligosaccharides with a lower degree of polymerisation (DP), including maltose (DP2), maltotriose (DP3), maltotetraose (DP4), and higher molecular weight species. In a single dose study, DP2, DP3 and DP4 showed a progressive rise in plasma concentrations with a profile similar to that for total icodextrin, with peak values reached by the end of the dwell and declining thereafter. Only very small increases in blood levels of larger polymers were observed. Steady-state plasma levels of icodextrin metabolites were achieved within one week and stable plasma levels were observed during long-term administration. Steady state plasma levels of 1.8mg/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. The long term effects of raised plasma levels of maltose and glucose polymer are unknown.

Some degree of metabolism of icodextrin occurs intraperitoneally with a progressive rise in the concentration of the smaller polymers in the dialysate during the 12-hour dwell. These fragments are cleared by peritoneal dialysis.

Icodextrin undergoes renal elimination in direct proportion to the level of residual renal function. Diffusion of the smaller icodextrin metabolites from plasma into the peritoneal cavity is also possible after systemic absorption and metabolism of icodextrin.

**CLINICAL TRIALS:** EXTRANEAL has demonstrated efficacy, as a peritoneal dialysis solution in clinical trials of approximately 400 patients studied with end-stage renal disease (ESRD). In active-controlled trials of one to six months in duration, EXTRANEAL used once-daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration compared with 1.5% and 2.5% dextrose solutions, and higher creatinine and urea nitrogen clearances when compared to 2.5% dextrose. Net ultrafiltration was similar to 4.25% dextrose. There is no information on how creatinine and urea nitrogen clearances on EXTRANEAL compared with 4.25% dextrose. Effects were generally similar in CAPD and APD. These studies were conducted in male and female patients > 18 years of age. Survival analysis was not included in these protocols. Ultrafiltration (UF) was the primary efficacy endpoint for all three of the pivotal studies. The studies only evaluated the effects of EXTRANEAL on ultrafiltration for the long dwell; the effects on 24 hour ultrafiltration are unknown.

**CLINICAL EFFICACY STUDIES**

Study Description	Study Results			
<b>RD-97-CA-130</b> double-blind, comparing efficacy (UF)* and safety of 7.5% icodextrin (N=90) with 2.5% dextrose (N=85) for the overnight (8-15 hour) dwell in CAPD patients for 4 weeks.	<b>The icodextrin group had a statistically significant greater net UF for the long dwell compared to dextrose (p = 0.001).</b>			
	Ultrafiltration Volumes			
	Baseline	Treatment (week 4)		
	Ico	control	Ico	control
	261	328	605	379
Creatinine and urea clearances were higher with icodextrin than 2.5% dextrose (p<0.001).				

**CLINICAL EFFICACY STUDIES** Continued

<p><b>ML/IB/001</b> Open label study comparing the efficacy (UF) and safety of 7.5% Icodextrin (N=106) with that of dextrose (N =103) for the long overnight dwell (8-12 hours) in CAPD patients for 6 months.</p> <p>*Patients Baseline UF was the UF measured with the solution (1.5% or 2.5%/4.25%) that they were using during the 2 week interval prior to being assigned to icodextrin or control (i.e. continue with their usual solution either 1.5% or 2.5%/4.25%).</p>	<p><b>Greater UF was seen in the icodextrin group compared to the 1.5% dextrose group (p=0.0002). No difference was found in the icodextrin group compared to the high (2.5% / 4.25%) dextrose group in an 8 and 12 hour-long dwell.</b></p>			
	Ultrafiltration Volume 8 hr dwell			
	Baseline*		Week 20	
	Ico	1.5%	Ico	1.5%
	61	76	517	153
	Ultrafiltration Volume 8 hr dwell			
	Baseline		Week 20	
	Ico	2.5/4.25%	Ico	2.5/4.25%
	711	614	462	465
	Ultrafiltration Volume 12 hr dwell			
	Baseline		Week 21	
	Ico	1.5%	Ico	1.5%
61	76	561	102	
Ultrafiltration Volume 12 hr dwell				
Baseline		Week 21		
Ico	2.5/4.25%	Ico	2.5/4.25%	
711	614	553	414	
<p><b>Pro-Renal-Reg-035</b> Open-label, randomised, parallel group, active-controlled study to compare the efficacy (UF)* and safety of EXTRANEAL (7.5% icodextrin) (N=20) with that of 2.5% dextrose (N=19) for the long daytime dwell (12-16 hours) in APD patients for 4 months.</p>	Icodextrin produced greater UF compared to baseline (p=0.001) and compared with dextrose (p=0.001).			
	Ultrafiltration Volume			
	Baseline		Week 12	
	Ico	control	Ico	control
	- 175	- 135	206	-166
Creatinine and urea clearances were higher in the icodextrin group compared to the dextrose group.				

\*UF = Ultrafiltration

**(iv) Indications:**

EXTRANEAL (7.5% icodextrin) is indicated for use as an alternative osmotic agent in dialysis solutions for the long dwell exchange in patients treated with peritoneal dialysis.

**(v) Contraindications:**

EXTRANEAL should not be used in 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 contraindicated 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.

**WARNING:** There have been reported deaths associated with hypoglycaemia and hypoglycaemic incidents that have resulted in permanent neurological damage. This is the result of falsely high blood glucose readings due to the interaction between Icodextrin and its by-products and glucometers that use pyrroloquinolinequinone (GDH-PQQ) for measuring blood glucose. Blood glucose measurement in patients receiving EXTRANEAL must be done with a glucose specific method (monitor and test strips) to avoid interference by maltose, released from EXTRANEAL. Glucose dehydrogenase

pyrroloquinolinequinone (GHD-PQQ)- based methods must not be used. The manufacturer(s) of the monitor and test strips should be contacted to determine if Icodextrin or maltose causes interference or falsely elevated glucose.

The manufacturer(s) of the monitor and test strips should be contacted to determine if Icodextrin or maltose causes interference or falsely elevated glucose.

**(vi) Precautions:**

**Use with caution in the following circumstances –**

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.

All peritoneal dialysis solutions, including EXTRANEAL, should be used with caution in patients with a history of abdominal surgery within 30 days of commencement of therapy, abdominal fistulae, tumours, open wounds, hernia or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity. As with other peritoneal dialysis fluids, EXTRANEAL should be used with caution, after careful evaluation of its potential risks and benefits, in patients with conditions that preclude normal nutrition, with impaired respiratory function or potassium deficiency.

Patients should be carefully monitored to avoid over and under hydration. An accurate fluid balance record should be kept and the patients 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.

In patients with hypercalcaemia, particularly in those on low-calcium peritoneal dialysis solutions, consideration should be given to the fact that EXTRANEAL is not provided in a low-calcium electrolyte solution.

Solutions that are cloudy, contain particulate matter, or show evidence of leakage should not be used.

Patients with insulin-dependent diabetes may require modification of insulin dosage following initiation of treatment with EXTRANEAL. Appropriate monitoring of blood glucose should be performed and insulin dosage adjusted if needed.

**Blood glucose measurement must be done with a glucose specific method to prevent maltose interference. Glucose dehydrogenase-based methods 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 WARNING and Effects on Laboratory Tests).

Aseptic technique should be employed throughout the peritoneal dialysis procedure. If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of culture and sensitivity of the isolated organisms. Prior to identification of involved organisms, broad-spectrum antibiotics may be indicated.

To reduce discomfort on administration, the solution may be warmed in the over pouch to a temperature of 37°C prior to use. This should be done using dry heat, ideally within a warming cabinet. The bags should not be immersed in water nor should they be microwaved in order to warm due to the potential for patient injury or discomfort.

Treatment should be initiated and monitored under the supervision of a physician knowledgeable in the management of patients with renal failure.

Pregnancy should be excluded prior to therapy with EXTRANEAL. A reliable method of contraception should be used by women of reproductive age, should they require long term treatment with EXTRANEAL.

Not for intravenous injection.

EXTRANEAL is intended for intraperitoneal administration only.

### Check the following before use –

EXTRANEAL is not recommended during pregnancy or lactation, in children or in patients with acute renal failure.

This therapy is not recommended in patients with known allergy to starch based polymers or an Icodextrin intolerance.

EXTRANEAL should not be used if there is a history of abdominal surgery in the month preceding commencement of therapy or if the patient is suffering from any of the following conditions affecting their abdomen: tumours, open wounds or herniae.

EXTRANEAL should not be used when acute renal failure has been diagnosed.

### Carcinogenicity, mutagenicity and impairment of fertility –

Long term carcinogenicity studies of icodextrin have not been done. Icodextrin was not mutagenic in a bacterial gene mutation assay, and was not clastogenic in V79 Chinese hamster lung cells in vitro or in mouse bone marrow cells in vivo. Potential effects on male and female fertility are unknown.

### Use in pregnancy –

**Category B2.** The potential effects of EXTRANEAL on reproduction have not been adequately studied in animals. There is insufficient experience with the use of dialysis fluids in pregnant women.

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

### Use in lactation -

There are no available data from animal studies on the effects of icodextrin administered during lactation. It is not known whether icodextrin and/or its metabolites are excreted into human milk. Because many drugs are excreted into human milk and because of the potential of adverse effects on the infants, EXTRANEAL should not be used in breastfeeding women.

### Interactions with other drugs -

None known - however, the blood concentrations of dialyzable 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.

### Effects on laboratory tests –

The safety and efficacy of EXTRANEAL was established via laboratory tests conducted on a patient study of over 200 individuals. A study of the results show that Icodextrin use produced a greater ultrafiltration volume compared to weak 1.36% glucose and was as effective as the stronger (3.86%) glucose. The mean overnight ultrafiltration was 3.5 times greater than 1.36% glucose at 8 hours and 5.5 times greater at 12 hours. No significant difference was observed at 8 or 12 hours comparing Icodextrin to 3.86% glucose.

Extending the dwell time from 8 to 12 hours tended to reduce net ultrafiltration with glucose 1.36% but increase it with Icodextrin. In addition 9 - 41% of patients on glucose (1.36 and 3.86%) experienced reabsorption of peritoneal dialysis fluid.

A subgroup analysis of diabetic patients showed that overall diabetic control and insulin requirements were not different in the icodextrin and glucose groups.

An increase in volume of ultrafiltrate after an 8 hour overnight dwell was seen in all patients when going from 1.36% glucose to icodextrin.

Decreases in serum sodium and chloride have been observed in patients using EXTRANEAL. The mean change in serum sodium from baseline to the last study visit was -2.8 mmol/L for patients on EXTRANEAL and -0.3 mmol/L for patients on control solution. Four EXTRANEAL patients and two control patients developed serum sodium < 125 mmol/L. The mean change in serum chloride from baseline to last study visit was -2.0 mmol/L for EXTRANEAL patients and + 0.6 mmol/L for control patients. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma. Although these decreases have been small and clinically unimportant, monitoring of the patients'

serum electrolyte levels as part of routine blood chemistry testing is recommended.

EXTRANEAL does not contain potassium. Evaluation of serum potassium should be made prior to administering potassium chloride to the patient.

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving EXTRANEAL. No associated increases in liver function tests were observed. Serum alkaline phosphatase levels did not show evidence of progressive increase over a 12- month study period. Levels returned to normal approximately two weeks after discontinuation of EXTRANEAL.

There were individual cases where increased alkaline phosphatase was associated with elevated AST (SGOT), but neither elevation was considered causally related to treatment.

A apparent decrease in serum amylase activity has been observed in patients using EXTRANEAL.

Blood glucose measurement must be done with a glucose-specific method to prevent maltose interference with test results. Since falsely elevated glucose levels have been observed with blood glucose monitoring devices and test strips that use glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ)-based methods or Glucose-dye-oxidoreductase methods, GDH-PQQ-based methods should not be used to measure glucose levels in patients administered EXTRANEAL. (See WARNING and Precautions).

### Ability to Drive and Use Machinery

Patients on peritoneal dialysis may experience undesirable effects, which could affect the ability to drive or use machines.

### (vii) Adverse Reactions:

**Blood glucose measurement with EXTRANEAL must be done with a glucose-specific method to avoid interference resulting in unrecognised hypoglycemia. If non-specific glucose test methods (GDH-PQQ or Glucose-dye-oxidoreductase based methods) are used, loss of consciousness, neurological damage or death may occur. This is a result of falsely high blood glucose readings due to the interaction between Icodextrin and its by-products to glucometers that use pyrroloquinolinequinone (GDH-PQQ) or Glucose-dye-oxidoreductase based methods for measuring blood glucose.**

A listing of adverse events reported in clinical studies, regardless of causality, occurring in ≥ 5% of patients and more common on EXTRANEAL is presented in Table 1.

Table 1 – Adverse Experience in ≥ 5% of Patients And More Common on EXTRANEAL

	EXTRANEAL N=493	Control N=347
Peritonitis	26%	25%
Upper respiratory infection	15%	13%
Hypertension	13%	8%
Rash	10%	5%
Headache	9%	7%
Abdominal Pain	8%	6%
Flu Syndrome	7%	6%
Nausea	7%	5%
Cough increase	7%	4%
Oedema	6%	5%
Accidental injury	6%	4%
Chest Pain	5%	4%
Dyspepsia	5%	4%
Hyperglycaemia	5%	4%

Adverse reactions reported with an incidence of > 5% and at least as common on dextrose control included pain, asthenia, exit site infection, back pain, hypotension, diarrhoea, vomiting, nausea/vomiting, anaemia, peripheral oedema, hypokalemia, hyperphosphatemia, hypoproteinemia, hypervolemia, arthralgia, dizziness, dyspnea, skin disorder, pruritus.

Adverse reactions on EXTRANEAL also include anorexia/loss of appetite, blood volume decreased, constipation, muscle cramps, dehydration, disequilibrium syndrome, hypovolemia, serum osmolality increased, ultrafiltration increased, urine volume decreased, weight increased and weight decreased.

Additional adverse events occurring at an incidence of < 5% and that may or may not have been related to EXTRANEAL include: pain on infusion, abdominal enlargement, cloudy effluent, ultrafiltration decrease, postural hypotension, heart failure, hyponatremia, hypochloremia, hypercalcemia, hypoglycaemia, alkaline phosphatase increase, SGPT increase, SGOT increase, cramping, confusion, lung oedema, facial oedema, exfoliative dermatitis, eczema, vesicobullous rash, maculopapular rash, erythema multiforme, serum amylase decrease, catheter blockage, disturbed vision, electrolyte imbalance, fatigue, fluid imbalance.

All reported events are included except those already listed in Table 1, those not plausibly associated with EXTRANEAL, and those that were associated with the condition being treated or related to the dialysis procedure.

Other undesirable effects of peritoneal dialysis related to the procedure and/or the solution. - The following undesirable effects are often reported spontaneously and in the literature:

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), hypervolemia, hypovolemia, 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 test results.

Those which are generally related to peritoneal dialysis solutions are seen less frequently than those related to the procedure and include, electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia and hypercalcaemia), fainting, muscle cramping, respiratory symptoms associated with shortness of breath and weakness, anorexia/lack of appetite, asthenia, catheter blockage, constipation, disturbed vision, disequilibrium syndrome, dyspnea/shortness of breath, oedema, cloudy effluent, exfoliative dermatitis, fluid imbalance, hypertension, hypervolaemia, exit site infection, abdominal pain, peritonitis, aseptic peritonitis and rash.

In addition there have been common reports of skin reactions in patients treated with icodextrin, including rash and pruritus. Occasionally, these rashes have been associated with exfoliation. The incidence of rash considered to be related to treatment in pooled data from all clinical studies\* was 5.5% for EXTRANEAL treated patients compared with 1.7% in patients treated with dextrose solutions.

### Post Marketing Surveillance

Post Marketing Surveillance data worldwide show that there have been serious hypoglycaemic reactions associated with the use of EXTRANEAL and non-glucose specific measuring devices. These reactions have resulted in death (2 cases to May 2005), and other hypoglycaemic events from which the patient recovered.

To avoid these events a glucose specific blood glucose monitor must be used. (See WARNING.)

### (viii) Dosage and administration:

EXTRANEAL is recommended for use during the longest dwell period, which in CAPD is usually overnight and in Automated Peritoneal Dialysis (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).

Aseptic technique should be observed throughout the procedure.

To reduce discomfort on administration, the solution may be warmed in the over pouch to a temperature of 37°C prior to use. This should be done using dry heat, ideally within a warming cabinet. The bags should not be immersed in water nor should they be microwaved in order to warm.

The volume to be instilled should be given over a period of approximately 10 to 20 minutes at a rate that the patients finds comfortable.

For adult patients of normal body size the instilled volume should not exceed 2.0L. 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. (see Adverse Reactions)

### (ix) Overdosage:

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.

### (x) Presentation :

Container -

Standard Single Bag: Flexible PVC container in 1500mL, 2000mL, 2500mL and 3000mL volumes.

Twin Bag: Flexible PVC container in 1500mL, 2000mL, 2500mL and 3000mL volumes. A drainage bag is attached.

Currently 2500 mL container available for standard single bag and twin bag only.

Shelf Life - 2 years.

Store below 30°C.

Do not use unless the solution is clear and the bag undamaged.

Single Use only.

Any unused portion of dialysate should be discarded.

### (xi) Name and address of sponsor:

Baxter Healthcare Pty Ltd	Baxter Healthcare Ltd
1 Baxter Drive	PO Box 14 062
Old Toongabbie	Panmure
NSW 2146	Auckland
Australia	New Zealand

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AUST R: Single Bag	91344
Twin Bag	91430

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**Baxter**