EXTRANEAL

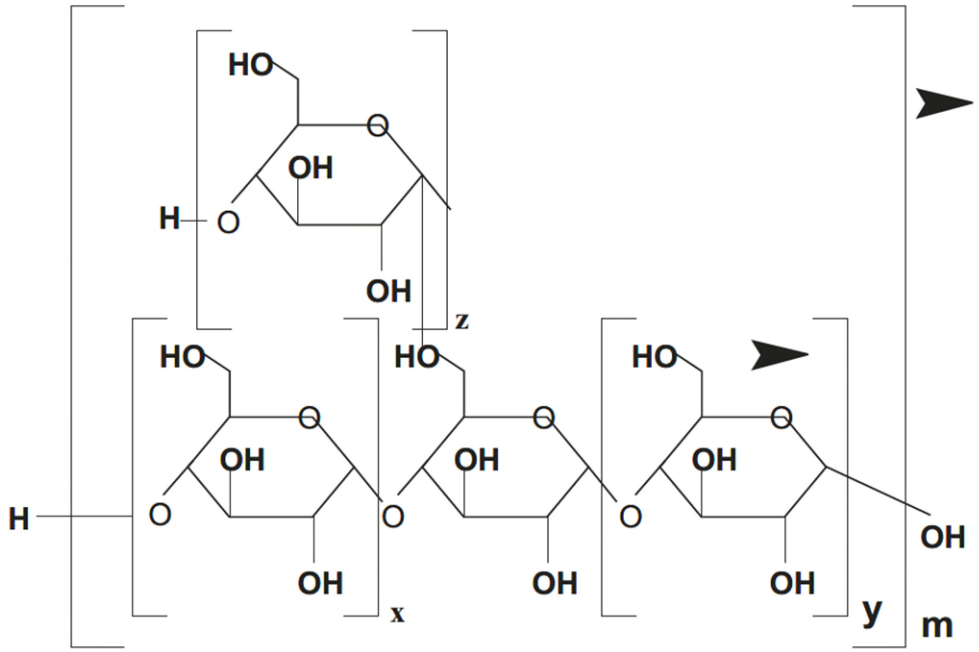
7.5% Icodextrin
Peritoneal dialysis solution

Composition
Each 100 ml of EXTRANEAL contains:

Icodextrin	7.5	g
Sodium chloride, USP	538	mg
Sodium lactate	448	mg
Calcium chloride, USP	25.7	mg
Magnesium chloride, USP	5.08	mg
Electrolyte content per liter:	132	mEq/l
Sodium	3.5	mEq/l
Calcium	0.5	mEq/l
Magnesium	96	mEq/l
Chloride	40	mEq/l
Lactate		

Water for injection, USP qs
HCl/NaOH may have been used to adjust pH.
EXTRANEAL contains no bacteriostatic or antimicrobial agents.Calculated osmolarity: 282-286 mOsm/l; pH=5.0-6.0

Description
EXTRANEAL (Icodextrin) Peritoneal Dialysis Solution is a peritoneal dialysis solution containing the colloid osmotic agent Icodextrin. Icodextrin is a starch-derived, water - soluble glucose polymer linked by alpha (1 - 4) and less than 10% alpha (1 - 6) glucosidic bonds with a weight - average molecular between 13,000 and 19,000 Daltons and a number average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of Icodextrin is:



EXTRANEAL is available for intraperitoneal administration only as a sterile,nonpyrogenic, clear solution in 2.0 l Ultrabag containers. The container systems are composed of polyvinyl chloride. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period,e.g. di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million; however,the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culturetoxicity studies.

Clinical pharmacology

Mechanism of action

EXTRANEAL is an isoosmotic peritoneal dialysis solution containing glucose polymers (Icodextrin) as the primary osmotic agent. Icodextrin function as a colloid osmotic agent to achieve ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in transcapillary ultrafiltration throughout the dwell. Like other peritoneal dialysis solutions, EXTRANEAL also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.

Pharmacokinetics of Icodextrin

Absorption

Absorption of Icodextrin from the peritoneal cavity follows zero-order kinetics consistent with convective transport via peritoneal lymphatic pathways. In a single-dose pharmacokinetic study using **EXTRANEAL**, 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.

Metabolism

Icodextrin is metabolized by alpha-amylase into oligosaccharides with a lower degree of polymerization (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. Some degree of metabolism of Icodetrin occurs intraperitoneally with a progressive rise in the concentration of the smaller polymers in the dialysate during the 12-hour dwell.

Elimination

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.

Special population

Geriatrics

The influence of age on the pharmacokinetics of Icodextrin and its metabolites was not assessed.

Gender and race

The influence of gender and race on the pharmacokinetics of Icodextrin and its metabolites was not assessed

Clinical studies

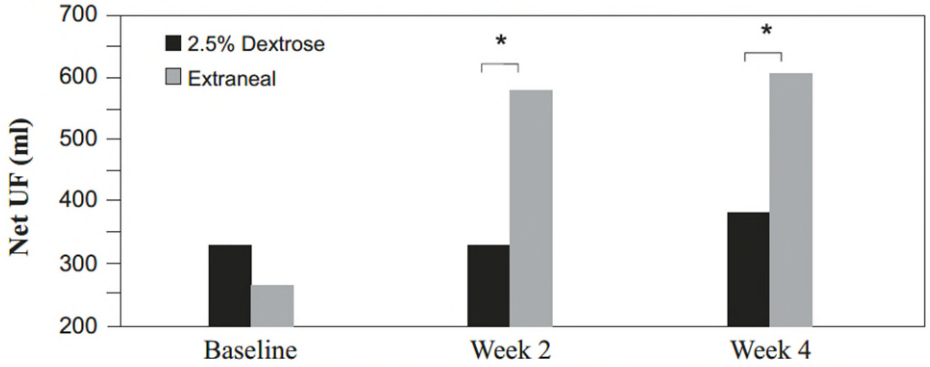
EXTRANEAL has demonstrated efficacy as a peritoneal dialysis solution in clinical trials of approximately 480 patients studied with end-stage renal disease (ESRD).

Ultrafiltration, urea and creatinine-clearance

In the active-controlled trials of one to six months in duration, described below, **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 than 1.5% and 2.5% dextrose solutions, and higher creatinine and urea nitrogen clearances than 2.5% dextrose. Net ultrafiltration was similar to 4.25% dextrose across all patients in these studies. Effects were generally similar in CAPD and APD.

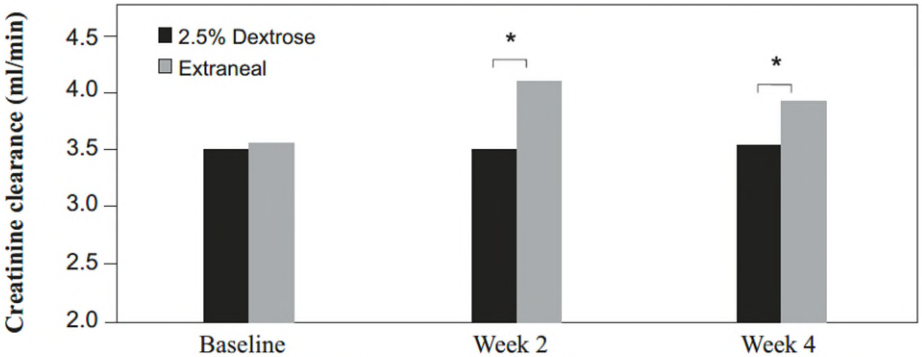
In an additional randomized, multicenter, active-controlled two-week study in high average/high transporter APD patients, **EXTRANEAL** used once daily for the long dwell produced higher net ultrafiltration compared to 4.25% dextrose. Mean creatinine and urea nitrogen clearances were also greater with **EXTRANEAL** and ultrafiltration efficiency was improved. In 175 CAPD patients randomized to **EXTRANEAL** (N = 90) or 2.5% dextrose solution (N = 85) for the 8-15 hour overnight dwell for one month, mean net ultrafiltration for the overnight dwell was significantly greater in the **EXTRANEAL** group at weeks 2 and 4 (Figure 1). Mean creatinine and urea nitrogen clearances were also greater with **EXTRANEAL** (Figure 2).

Figure 1 – Mean net ultrafiltration for the overnight dwell

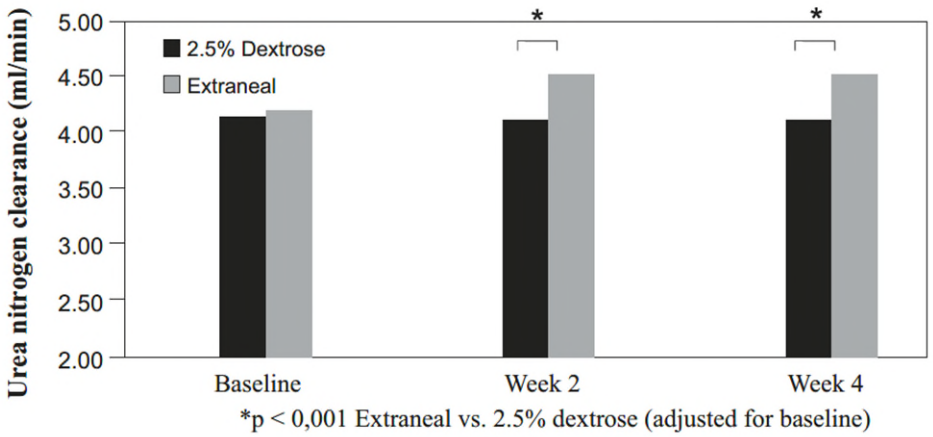


*p < 0,001 Extraneal vs. 2.5% dextrose (adjusted for baseline)

Figure 2 – Mean creatinine and urea nitrogen clearance for overnight dwell

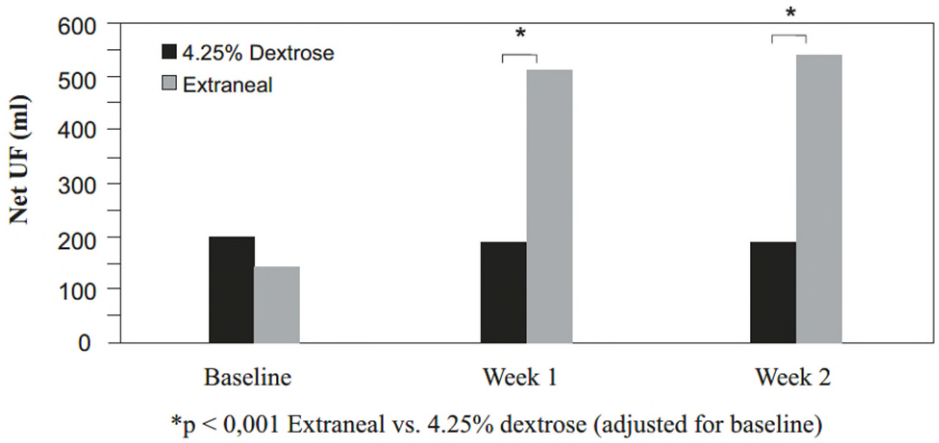


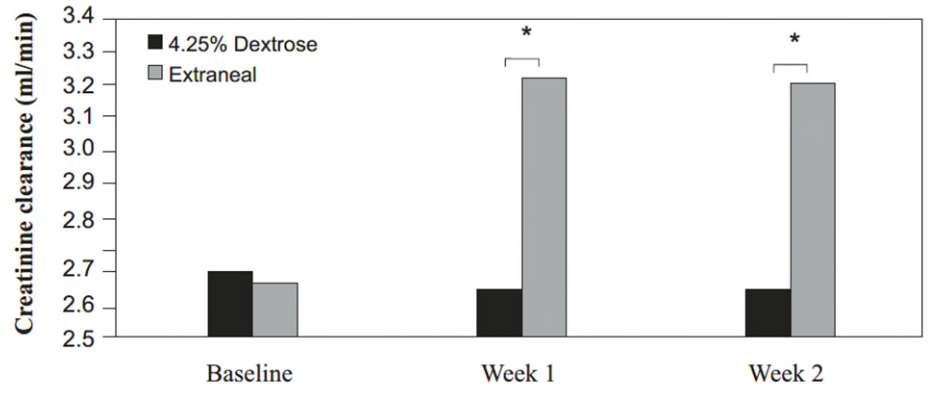
*p < 0,001 Extraneal vs. 2.5% dextrose (adjusted for baseline)



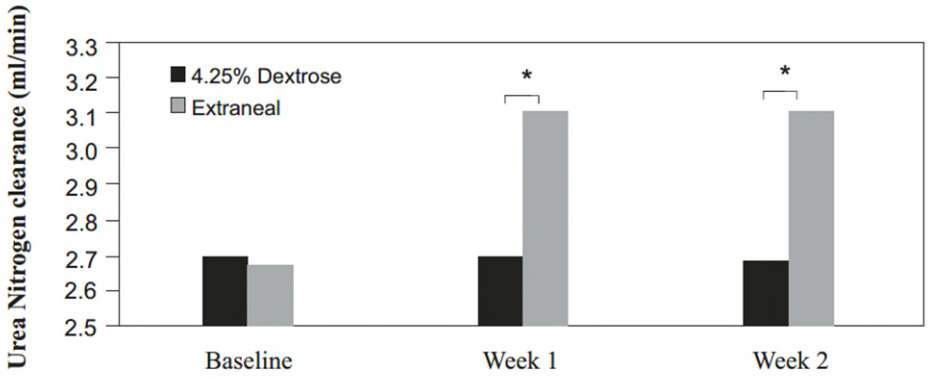
In another study of 39 APD patients randomized to **EXTRANEAL** or 2.5% dextrose solution for the long, daytime dwell (10 - 17 hours) for three months, the net ultrafiltration reported during the treatment period was (mean ± SD) 278 ± 192 ml for the **EXTRANEAL** group and - 138 ± 352 ml for the dextrose group ($p < 0.001$). Mean creatinine and urea nitrogen clearances were significantly greater for **EXTRANEAL** than 2.5% dextrose at weeks 6 and 12 ($p < 0.001$).
In a six-month study in CAPD patients comparing **EXTRANEAL** (n = 28)with 4.25% dextrose (n = 31), net ultrafiltration achieved during an 8 - hour dwell averaged 510 ml for **EXTRANEAL** and 556 ml for 4.25% dextrose.For 12-hour dwells, net ultrafiltration averaged 575 ml for **EXTRANEAL** (n= 29) and 476 mL for 4.25% dextrose (n = 31). There was no significant difference between the two groups with respect to ultrafiltration. In a two weeks study in high average / high transporter APD patients (4 - hour D/P creatinine ratio > 0.70 and a 4 - hour D / D0 ratio < 0.34 as defined by the peritoneal equilibration test (PET), comparing **EXTRANEAL** (n = 47) to
4.25% dextrose (n = 45), after adjusting for baseline, the mean net ultrafiltration achieved during a 14 ± 2 hours dwell was significantly greater in the **EXTRANEAL** group than the 4.25% dextrose group at weeks 1 and 2 ($p < 0.001$, see Figure 3). Consistent with increases in net ultrafiltration, there were also significantly greater creatinine and urea nitrogen clearances and ultrafiltration efficiency in the **EXTRANEAL** group ($p < 0.001$, see Figure 3).

Figure 3 – Mean net ultrafiltration, creatinine and urea nitrogen clearances and ultrafiltration efficiency for the long dwell in high average / high transporter patients

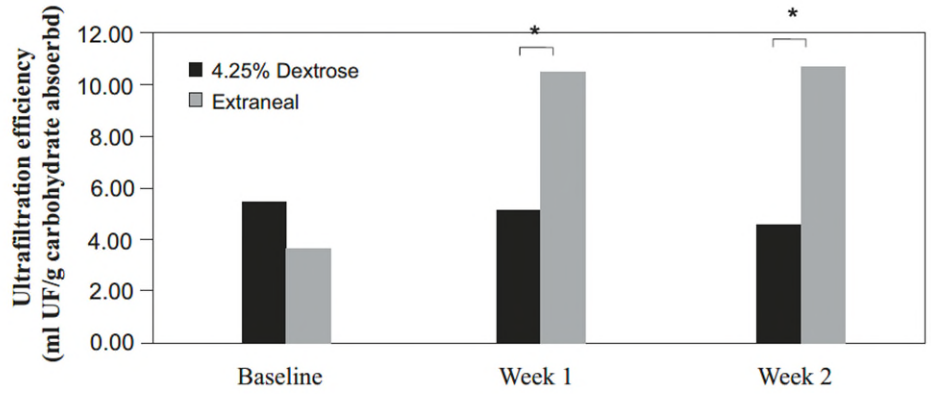




*p<0,001 Extraneal vs. 4.25% dextrose (adjusted for baseline)



*p<0,001 Extraneal vs. 4.25% dextrose (adjusted for baseline)



*p<0,001 Extraneal vs. 4.25% dextrose (adjusted for baseline)

Peritoneal membrane transport characteristics:
After one year of treatment with **EXTRANEAL** during the long dwell exchange, there were no differences in membrane transport characteristics for urea and creatinine. The mass transfer area coefficients (MTAC) for urea, creatinine, and glucose at one year were not different in patients receiving treatment with **EXTRANEAL** or 2.5% dextrose solution for the long dwell.

Indication and usage
EXTRANEAL is indicated for a single daily exchange for the long (8 - to 16 hours) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of end - stage renal disease. **EXTRANEAL** is also indicated to improve (compared to 4.25% dextrose) long-dwell ultrafiltration and clearance of creatinine and urea nitrogen in patients with high average or greater transport characteristics, as defined using the peritoneal equilibration test (PET). (See **Clinical pharmacology, Clinical studies**).

Contraindications
EXTRANEAL is contraindicated in patients with a known allergy to cornstarch or Icodextrin, or in patients with glycogen storage disease.
EXTRANEAL is contraindicated in patients with a history of abdominal surgery in the month proceeding commencement of therapy of suffering from abdominal fistulae (non-healing weeping wounds), tumours, open wounds, herniae or other conditions affecting the abdomen.

Dosage and administration
EXTRANEAL is intended for intraperitoneal administration only. It should be administered only as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. The recommended dwell time is 8- to 16- hours. Patients should be carefully monitored to avoid under- or over-hydration. An accurate fluid balance record must be kept and the patient's body weight monitored to avoid potentially severe consequences including congestive heart failure, volume depletion, and hypovolemic shock.
Aseptic technique should be used throughout the peritoneal dialysis procedure.
To reduce possible discomfort during administration, solutions may be warmed prior to use. (See **Dosage and administration, Directions for use**).
EXTRANEAL should be administered over a period of 10 - 20 minutes at a rate that is comfortable for the patient.
Do not use **EXTRANEAL** if it is cloudy or discolored, if it contains particulate matter, or if the container is leaky. Following use, the drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of an infection.

Addition of potassium
Potassium is omitted from **EXTRANEAL** solutions because dialysis maybe performed to correct hyperkalemia. In situations where 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. The decision to add potassium chloride should be made by the physician after careful evaluation of serum potassium.

Addition of insulin
Addition of insulin to **EXTRANEAL** was evaluated in 6 insulin-dependent diabetic patients undergoing CAPD for end stage renal disease. No interference of **EXTRANEAL** with insulin absorption from the peritoneal cavity or with insulin's ability to control blood glucose was observed. (See **Precautions, Drug/Laboratory test interactions**). Appropriate monitoring of blood glucose should be performed when initiating **EXTRANEAL** in diabetic patients and insulin dosage adjusted if needed (See **Precautions**).

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

Addition of antibiotics
No formal clinical drug 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.
Patients undergoing peritoneal dialysis should be under careful supervision of a physician experienced in the treatment of end-stage renal disease with peritoneal dialysis. It is recommended that patients being placed on peritoneal dialysis should be appropriately trained in a program that is under supervision of a physician.

Directions for use
For complete CAPD and APD system preparation, see directions accompanying ancillary equipment. Aseptic technique should be used.

Warming
For patient comfort, **EXTRANEAL** can be warmed to 37°C (98°F). Only dry heat should be used. It is best to warm solutions within the overwrap using a heating pad. Do not immerse **EXTRANEAL** in water for warming. Do not use a microwave oven to warm **EXTRANEAL.**
Heating above 40°C (104°F) may be detrimental to the solution.

To open
To open, tear the overwrap down at the slit and remove the solution container. Some opacity of the plastic, due to moisture absorption during the sterilization process, may be observed.
This does not affect the solution quality or safety and may often leave a slight amount of moisture within the overwrap.

Inspect for container integrity
Inspect the container for signs of leakage and check for minute leaks by squeezing the container firmly.

Adding medications
Some drug additives may be incompatible with **EXTRANEAL**. (See **Dosage and administration** section for additional information). If the re-sealable rubber plug on the medication port is missing or partly removed, do not use the product if medication is to be added.
1. Prepare medication port site.
2. Using a syringe with a 1-inch long, 25- to 19-gauge needle, puncture the medication port and inject additive.
3. Reposition container with container ports up and evacuate medication port by squeezing and tapping it.
4. Mix container thoroughly.

Preparation for administration
1. Place **EXTRANEAL** on flat surface or suspend from support (depending on ancillary equipment).
2. Remove protector from outlet port on container.
3. Refer to complete instructions with ancillary equipment or transfer set.
4. Discard any unused portion.

Warnings
Not for intravenous injection.
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 (GDH PQQ) or glucose-dye-oxidoreductase based methods must 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 hypoglycemia, 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 hypoglycemia and allow it to go untreated with similar consequences. **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.**

Precautions
General
Peritoneal dialysis - related
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, tumors, open wounds, hernia or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity. Caution should also be used in patients with conditions that preclude normal nutrition, patients with impaired respiratory function, and patients with potassium deficiency.

Aseptic technique should be employed throughout the peritoneal dialysis procedure to reduce the possibility of infection. 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.

Need for trained physician
Treatment should be initiated and monitored under the supervision of a physician knowledgeable in the management of patients with renal failure. A patient's volume status should be carefully monitored to avoid hyper or hypovolemia and potentially severe consequences including congestive heart failure, volume depletion and hypovolemic shock. An accurate fluid balance record must be kept and the patient's body weight monitored. Significant losses of protein, amino acids, and water-soluble vitamins mayoccur during peritoneal dialysis. The patient's nutritional status should be monitored and replacement therapy should be provided as necessary.

In patients with hypercalcemia, 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.

Insulin - dependent diabetes mellitus
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 (See **Warnings; Precautions, Drug/Laboratory test interactions**).

Information for patients
Patients should be instructed not to use solutions if they are cloudy, discolored, contain visible particulate matter, or if they show evidence of leaking containers.

Aseptic technique should be employed throughout the procedure.

To reduce possible discomfort during administration, patients should be instructed that solutions may be warmed to 37°C (98°F) prior to use. Only dry heat should be used. It is best to warm solutions within the over wrap using a heating pad. To avoid contamination, solutions should not be immersed in water for warming. Do not use a microwave oven to warm **EXTRANEAL**. Heating the solution above 40°C (104°F) may be detrimental to the solution. (See **Dosage and administration, Directions for use**).

Because the use of **EXTRANEAL** interferes with glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) and glucose-dye-oxidoreductase based blood glucose measurements, patients should be instructed to use only glucose-specific glucose monitors and test strips. (See **Warnings; Precautions, Drug / Laboratory test interactions**).

Additional information for patients is provided at the end of the labeling.

Laboratory tests
Serum electrolytes
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 -0.3mmol/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. Similar changes in serum chemistries were observed in an additional clinical study in a subpopulation of high average / high transporter 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.

Alkaline phosphatase
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.

Adverse reactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. **EXTRANEAL** was originally studied in controlled clinical trials of 493 patients with end-stage renal disease who received a single daily exchange of **EXTRANEAL** for the long dwell (8-to 16- hours). There were 215 patients exposed for at least 6 months and 155 patients exposed for at least one year. The population was 18-83 years of age, 56% male and 44% female,73% Caucasian, 18% Black, 4% Asian, 3% Hispanic, and it included patients with the following comorbid conditions: 27% diabetes, 49% hypertension and 23% hypertensive nephropathy.
Rash was the most frequently occurring **EXTRANEAL** - related adverse event (5.5%, **EXTRANEAL**; 1.7% Control). Seven patients on **EXTRANEAL** discontinued treatment due to rash, and one patient on **EXTRANEAL** discontinued due to exfoliative dermatitis. The rash typically appeared within the first three weeks of treatment and resolved with treatment discontinuation or, in some patients, with continued treatment. Female patients reported a higher incidence of skin events, including rash, in both **EXTRANEAL** and dextrose control treatment groups.
Table 1 shows the adverse events reported in these clinical studies, regardless of causality, occurring in ≥ 5% of patients and more common on **EXTRANEAL** than control.

Table 1 - Adverse experiences in ≥ 5 % of patients and more common on EXTRANEAL

	EXTRANEAL	Control
	N = 493	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%
Edema	6%	5%
Accidental injury	6%	4%
Chest pain	5%	4%
Dyspepsia	5%	4%
Hyperglycemia	5%	4%

Adverse reactions reported with an incidence of > 5% and at least as common on dextrose control included pain, asthenia, exit site infection, infection, back pain, hypotension, diarrhea, vomiting, nausea/vomiting, anemia, peripheral edema, hypokalemia, hyperphosphatemia hypoproteinemia, hypervolemia, arthralgia, dizziness, dyspnea, skin disorder, pruritis.
Additional adverse events occurring at an incidence of < 5% and that mayor may not have been related to **EXTRANEAL** include: pain on infusion, abdominal enlargement, cloudy effluent, ultrafiltration decrease, postural hypotension, heart failure, hyponatremia, hypochloremia, hypercalcemia, hypoglycemia, alkaline phosphatase increase, SGPT increase, SGOT increase, cramping, confusion, lung edema, facial edema, exfoliative dermatitis, eczema, vesicobullous rash, maculopapular rash, erythema multiforme. All reported events are included in the list except those already listed in Table 1 or the following two paragraphs, those not plausibly associated with **EXTRANEAL**, and those that were associated with the condition being treated or related to the dialysis procedure. **EXTRANEAL** was additionally studied in a subpopulation of 92 high average/high transporter APD patients in a two-week controlled clinical trial where patients received a single daily exchange of **EXTRANEAL** (n=47)or dextrose control (n=45) for the long dwell (14 ± 2 hours). Consistent with the data reported in the original trials of **EXTRANEAL**, rash was the most frequently occurring event.

Peritoneal dialysis - related
Adverse events common to the peritoneal dialysis, including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain, were observed at a similar frequency with **EXTRANEAL** and controls (See Precautions).

Changes in alkaline phosphatase and serum electrolytes
An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving **EXTRANEAL**. No associated increases in other liver chemistry tests were observed. Serum alkaline phosphatase levels did not show progressive increase over a 12-monthstudy period. Levels returned to normal approximately two weeks after discontinuation of **EXTRANEAL**.
Decreases in serum sodium and chloride have been observed in patients using **EXTRANEAL**. 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 patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

Drug interactions

General

No clinical drug interaction studies were performed. No evaluation of **EXTRANEAL's** effects on the cytochrome P450 system was conducted. As with other dialysis solutions, blood concentrations of dialyzable drugs may be reduced by dialysis. Dosage adjustment of concomitant medications may be necessary. In patients using cardiac glycosides (Digoxin and others),plasma levels of calcium, potassium and magnesium must be carefully monitored.

Insulin

A clinical study in 6 insulin-dependent diabetic patients demonstrated no effect of **EXTRANEAL** on insulin absorption from the peritoneal cavity or on insulin's ability to control blood glucose when insulin was administered intraperitoneally with **EXTRANEAL.**

However, appropriate monitoring (See **Precautions, Drug/Laboratory test Interactions**) of blood glucose should be performed when initiating **EXTRANEAL** in diabetic patients and insulin dosage should be adjusted if needed (See **Precautions**).

Heparin

No human drug interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with **EXTRANEAL.**

Antibiotics

No human drug interaction studies with antibiotics were conducted. In vitro studies evaluating the minimum inhibitory concentration (MIC) of Vancomycin, Cefazolin, Ampicillin, Ampicillin/ Flucoxacillin, Ceftazidime, gentamicin, and amphotericin demonstrated no evidence of incompatibility of these antibiotics with **EXTRANEAL**. (See **Dosage and administration**).

Drug/Laboratory test interactions

Blood glucose

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) or glucose-dye-oxidoreductase based methods, GDH PQQ or glucose-dye-oxidoreductase based methods should not be used to measure glucose levels in patients administered **EXTRANEAL**. (See **Warnings**).

Serum amylase

An apparent decrease in serum amylase activity has been observed inpatients administered **EXTRANEAL**. Preliminary investigations indicate that Icodextrin and its metabolites interfere with enzymatic-based amylase assays, resulting in inaccurately low values. This should be taken into account when evaluating serum amylase levels for diagnosis or monitoring of pancreatitis in patients using **EXTRANEAL**.

Carcinogenesis, Mutagenesis, Impairment of fertility

Icodextrin did not demonstrate evidence of genotoxicity potential in in vitro bacterial cell reverse mutation assay (Ames test); in vitro mammalian cell chromosomal aberration assay (CHO cell assay); and in the in vivo micronucleus assay in rats. Long-term animal studies to evaluate the carcinogenic potential of **EXTRANEAL** or Icodextrin have not been conducted. Icodextrin is derived from Maltodextrin, a common food ingredient. A fertility study in rats where males and females were treated for four and two weeks, respectively, prior to mating and until day 17 of gestation at up

to 1.5 g/kg/day (1/3 the human exposure on a mg/m2 basis) revealed slightly low epididymal weights in parental males in the high dose group as compared to control. Toxicological significance of this finding was not evident as no other reproductive organs were affected and all males were of proven fertility. The study demonstrated no effects of treatment with Icodextrin on mating performance, fertility, litter response, embryo-fetal survival, or fetal growth and development.

Pregnancy

Pregnancy category C

Complete animal reproduction studies including in utero embryo fetal development at appreciable multiples of human exposure have not been conducted with **EXTRANEAL** or Icodextrin. Thus it is not known whether Icodextrin or **EXTRANEAL** solution can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. **EXTRANEAL** should only be utilized in pregnant women when the need outweighs the potential risks.

Nursing mothers

It is not known whether Icodextrin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **EXTRANEAL** is administered to a nursing woman.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

Geriatric use

No formal studies were specifically carried out in the geriatric population. However, 140 of the patients in clinical studies of **EXTRANEAL** were age 65 or older, with 28 of the patients age 75 or older. No overall differences in safety or effectiveness were observed between these patients and patients under age 65. Although clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Drug abuse and dependence

There has been no observed potential of drug abuse or dependence with **EXTRANEAL.**

Overdosage

No data are available on experiences of overdosage with **EXTRANEAL**. Overdosage of **EXTRANEAL** would be expected to result in higher levels of serum Icodextrin and metabolites, but it is not known what signs or symptoms might be caused by exposure in excess of the exposures used in clinical trials. In the event of overdosage with **EXTRANEAL**, continued peritoneal dialysis with glucose-based solutions should be provided.

Packaging
Extraneal : Ultrabag @ : 2.0 L
Reg. No. DKI0915600242A1

Store below 30°C.
Store in moisture barrier overwrap in carton until ready to use. Protect from freezing.

ON MEDICAL PRESCRIPTION ONLY.
HARUS DENGAN RESEP DOKTER.

Manufactured by:
BAXTER HEALTHCARE SA, SINGAPORE BRANCH
2 Woodlands Industrial Park D, Singapore 738750
Imported and marketed by:
PT KALBE FARMA Tbk.
Bekasi - Indonesia