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TO: NDA 21-321, 7.5% Icodextrin Peritoneal Dialysis Solution

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Subject: Medical Review

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EXECUTIVE SUMMARY

Chronic ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are currently performed using Dextrose in various concentrations as the osmotic agent to remove excess fluid and waste products from the system of End Stage Renal Disease (ESRD) patients. Because the osmotic gradient across the peritoneum decreases with Dextrose over the course of a long-dwell dialysis, Baxter has developed a different drug, Icodextrin, designed to maintain the gradient over the long-dwell period of peritoneal dialysis, and therefore increase the efficiency of dialysis.

Icodextrin is a high molecular weight glucose polymer derived from maltodextrin, and is administered with electrolytes. The dialysis solution contains 7.5 g per 100 ml, and 2.0 or 2.5 L are used for the long-dwell period of dialysis. Approximately 30-40% of Icodextrin is absorbed from a single exchange depending on dwell time (between 8-16 hours), and is systemically hydrolyzed to smaller oligosaccharides.

The clinical program compared the dialysis efficacy and safety to Dextrose for the long-dwell period in both CAPD and APD. No placebo controlled efficacy studies were performed.

Clinical studies 130, MIDAS and Pro-Renal demonstrated superiority of Icodextrin versus 1.5% or 2.5% Dextrose for net ultrafiltration and creatinine and urea clearance in long-dwell CAPD or APD. Superiority of Icodextrin versus 4.5% Dextrose was not demonstrated. Data to demonstrate that the increased ultrafiltration and creatinine and urea clearances benefited the patients clinically were not convincing, but it was clear that Icodextrin was an effective dialysis drug.

A serious safety concern was raised by study 131, a 52 week safety study with mortality as the primary endpoint, in which the mortality data were adverse for Icodextrin compared to Dextrose. In the 13 month post-enrollment follow-up results, there were 20 Icodextrin deaths (n=175, 11.4%) and 9 Dextrose deaths (n=112, 8%). Review of each case and exploratory subgroup analyses did not provide an explanation for the numerically adverse result. A pooling of all known deaths from all controlled trials did not replicate the adverse finding in study 131. Nevertheless, that result remains a concern.

Other adverse findings associated with Icodextrin were rash, decreased serum sodium and chloride, elevated alkaline phosphatase and AST (SGOT). A decline in serum amylase due to assay interference, and a slight decline in serum cholesterol was noted. No difference in effect on serum glucose, insulin requirements or HgA1C was found between treatments.

Considering the safety and efficacy data, a recommendation for approval for those patients inadequately responding to CAPD or APD with Dextrose for the long-dwell period is made. A post-marketing, long term, active-controlled, randomized mortality study should be considered.

CLINICAL REVIEW

I. INTRODUCTION and BACKGROUND

On 12/20/2000, Baxter Healthcare Corporation submitted an NDA for Extraneal (7.5% Icodextrin with electrolytes) peritoneal dialysis solution for the treatment of chronic renal failure. The drug is a designated orphan drug. The total submission consists of 155 volumes, SAS data sets for the Phase III clinical trials, and pdf files for the case report forms. Certifications re financial interests and arrangements with clinical investigators, and patent information covering the formulation, composition and/or method of use are included.

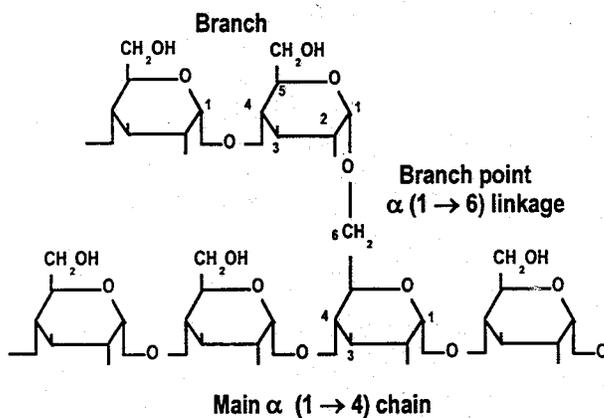
The medical portion of the submission includes volumes 1.1, 1.23-1.76 and 1.39A, and amendments dated 3/20/2001, 4/5/2001, 4/16/01, 4/18/01 and 5/3/01. On October 19,2000 a closed meeting of the CardioRenal Advisory Committee was held to discuss development of peritoneal dialysis solutions, at which meeting some of the data contained in this application was discussed. As a result of that discussion some additional data was gathered, analyzed and included in the application i.e. follow-up status of patients who participated in study RD 97-CA-131, a one year randomized safety study.

The drug is a new molecular entity, and has been approved in 17 European countries including the UK as well as in Canada. It is a designated orphan drug.

II. CLINICALLY RELEVANT INFORMATION RE: CHEMISTRY and NON-CLINICAL PHARMACOLOGY and TOXICOLOGY

1. Chemistry

Icodextrin is a soluble glucose polymer derived from maltodextrin that in turn was derived by partial hydrolysis of starch. It has an average molecular weight of 12000-20000 Daltons, and its molecular structure is represented as follows:



It is formulated as a 7.5% aqueous solution with electrolytes, and is manufactured by ML laboratories, PLC of Liverpool, England. The proposed fill volumes for various containers is 1.5L, 2.0L, and 2.5L. For the US, the composition of the electrolyte solution would be the same as for the currently available Dianeal PD-2 . The formulation proposed for marketing is:

<u>COMPONENT</u>	<u>COMPOSITION / 100 mL</u>
Icodextrin	7.5 g
Sodium Chloride, USP	535* mg
Sodium Lactate	448 mg
Calcium Chloride Dehydrate, USP	25.7 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Hydrochloric acid	for pH adjustment
Sodium Hydroxide	for pH adjustment
Water for Injection, USP	qs

Approximate mEq per liter:

Lactate	40
Sodium	132
Calcium	3.5
Magnesium	0.5
Chloride	96

*Approximately 0.6 mEq/L of 1.0 N sodium hydroxide is required to adjust the pH of the drug product which is equal to approximately 3.5 mg of sodium chloride.

For further information, see chemistry review.

2. Non-Clinical Pharmacology and Toxicology

See Pharmacology review. Most studies were carried out using the ip route for 28 days, and blood levels were not detected in rats and low in dogs. A chart comparing those levels to man was provided as follows:

Species	Dose Details	Sample time (n)	Mean Plasma Levels (mg/ml)		
			G2	G3 - G10	G>10
Rat	4.0 & 6.0 g/kg IP twice daily for 28 days	Day 1:24h (4) Day 1:24h (4)	None detected		
Dog	6.0g/kg IP twice daily for 28 days (12g/kg/day)	Pre-dose (8) Day 1:5h (8) Day 1:24h (8) Day 21:5h (8) Day 21:24h (8) Day 28:5h (8) Day 1:24h (8)	0.02 0.11 0.02 0.05 0.02 0.03 0.02	0.02 0.52 0.22 0.33 0.24 0.28 0.26	0.10 0.17 0.13 0.18 0.16 0.14 0.16
Man (Davies,1994)	150 g once daily IP for 6 months (2.14 g/kg/day)	Pre-dose (91) 1 month (80) 3 months (72) 6 months (53)	0.04 1.20 1.00 1.06	0.02 1.84 1.67 1.76	0.29 1.83 1.73 1.84

No carcinogenicity tests were performed. Ames test, CHO test and mouse micronucleus test were performed and no genotoxicity was observed. A reproductive study by ML Laboratories was not included in the NDA. The sponsor notes that maltodextrin is classed as GRAS as a food ingredient. In metabolic animal studies it was shown that the route of elimination was renal, and icodextrin was hydrolyzed, probably by alpha amylase, to oligosaccharides including maltose and maltotriose.

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

One single-dose and several multiple-dose studies evaluated the PK of Icodextrin. See the Pharmacology review for details of those studies.

Since Icodextrin is directly instilled into the abdominal cavity, bioavailability is assured. In the abdominal cavity the drug works as a colloid osmotic agent to effect ultrafiltration in peritoneal dialysis. The osmotic pressure created by Icodextrin is thought to be relatively constant with little loss of osmotic gradient during long-dwells.

As noted in the preclinical section, Icodextrin is hydrolyzed by alpha amylase and smaller oligosaccharides such as maltose, maltotriose and maltotetraose have been quantified in the plasma. Maltase further metabolizes the oligosaccharides to glucose.

During daily Icodextrin administration in single, long-dwell exchanges, plasma levels of 4-6.5 g/L of Icodextrin were found within one week and remained constant. Steady-state plasma levels of maltose ranged from 0.81 to 1.35 g/L. Steady state plasma levels of maltotriose were similar to maltose levels, and only small increases in plasma levels of larger metabolites were found. From a single dose of 150 g of Icodextrin, approximately 30-40% was absorbed, depending on dwell time. After discontinuation the plasma levels of Icodextrin and metabolites return to baseline in one to two weeks. Absorption from the peritoneal cavity into the blood follows zero order kinetics, and the drug is renally excreted, depending on residual renal function.

IV. DESCRIPTION of CLINICAL DATA

Clinical Trials

a) The sponsor identified 4 pivotal clinical trials which are outlined in the following chart.

Study	Description	N	Duration	Endpoint(s)
RD-97-CA-130 Vol.1.31-1.37	Prospective, DB, Randomized comparison of Icodextrin and 2.5% Dextrose	Total=175 Ico=90 Dex=85 CAPD patients	4 weeks	Net UF
ML/1B/001 MIDAS Vol. 1.57-1.63	Open, Randomized comparison of Icodextrin and 1.5%,2.5%,4.5% Dextrose	Total=209 Ico=106 Dex=103 CAPD patients	6 months	Net UF
Pro-Renal-Reg-035 Vol. 1.54-1.56	Open, Randomized comparison of Icodextrin and 2.5% Dextrose	Total=39 Ico=20 Dex=19 APD patients	16 weeks	UF, Creatinine and Urea clearances
RD-97-CA-131 Vol. 1.38-1.53	Prospective, Randomized, DB Comparison of Icodextrin and 2.5% Dextrose	Total=287 Ico=175 Dex=112 CAPD and APD patients	52 weeks	Safety, Quality of Life

b) Supportive controlled clinical studies provided were:

ML/1B/004 (MIDAS-2): an open label long-term extension of MIDAS.

ML/1B/020 (DELIA): an open two-way crossover study comparing Icodextrin to a dry day.

ML/1B/011 (DIANA): an open, randomized comparison of Icodextrin to Dextrose in 38 APD patients for 2 years. 13 patients completed the 2 years.

RD-99-CA-060: an open single dose PK study of Icodextrin in a single exchange.

ML/1B/014: an open uncontrolled study of serum concentrations of drug and metabolites at steady state, after treatment cessation and after restarting.

ML/1B/002: an open randomized cross-over study of adding insulin to CAPD solutions in diabetics comparing Icodextrin and 1.5% glucose.

c) Cancelled studies due to slow enrollment were:

ML/1B/009 (IDEAL): an open, uncontrolled study that was to include 100 patients, but enrolled only 16 over more than a year.

PRO-RENAL-REF-037A: an open, uncontrolled study that was to include 80 patients but cancelled after 27 patients were enrolled. According to the sponsor analyses of the study are ongoing, and data were not included in the submission.

This review will consider the 4 pivotal studies in detail, and the others briefly.

V. CLINICAL REVIEW

Each of the clinical studies provided by the sponsor is summarized in the following clinical review.

1. RD-97-CA-130: This randomized, double-blind study of 7.5% Icodextrin peritoneal dialysis solution compared to 2.5% Dextrose peritoneal dialysis solution was initiated on April 1, 1998 and completed on December 29, 1998, and conducted in the US and Canada. Dianeal PD-2 was used in the US, and Dianeal PD-4 was used in Canada each with 2.5% Dextrose (2.27% glucose). The composition of the Icodextrin solution was:

COMPONENT	Composition/100 mL
Icodextrin	7.5 g
Sodium Chloride, USP	535 mg *
Sodium Lactate	448 mg
Calcium Chloride Dihydrate, USP	25.7 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Hydrochloric acid	for pH adjustment
Sodium Hydroxide	for pH adjustment
Water for Injection, USP	qs
COMPONENT	Approx. mEq/L
Lactate	40
Sodium	132
Calcium	3.5
Magnesium	0.5
Chloride	96

*Approximately 0.6 mEq/L of 1.0 N sodium hydroxide is required to adjust the pH of the drug product, which is equal to approximately 3.5 mg of sodium chloride.

That of the PD-2 and PD-4 solutions were:

COMPONENT	PD-2	PD-4
Composition per 100 mL		
Sodium chloride, USP	538 mg	538 mg
Sodium lactate	448 mg	448 mg
Calcium chloride dihydrate, USP	25.7 mg	18.3 mg
Magnesium chloride hexahydrate, USP	5.08 mg	5.08 mg
Dextrose hydrous, USP	2.5 g	2.5 g
Water for injection, USP	qs	qs
Approximate mEq per liter		
Lactate	40	40
Sodium	132	132
Calcium	3.5	2.5
Magnesium	0.5	0.5
Chloride	96	95

The solutions were provided in Ultrabag, Twinbag or single bag configurations and the fill volume for each long-dwell dialysis was 2.0 or 2.5 liters.

The study was designed as a non-inferiority trial which in the August 13, 1998 protocol amendment was defined as established if the difference between groups was within 30% of the mean ultrafiltration (UF) in the long-dwell exchange for the control group. In the original December 5, 1997 protocol the non-inferiority definition used a 95% one-sided confidence interval with a lower bound greater than 150 ml. Secondary variables were peritoneal urea nitrogen exchange and peritoneal creatinine clearance. 175 patients were randomized: 90 to Icodextrin and 85 to control. Patients 18 years of age or older who had been on CAPD for at least 90 days, and who were treated by a long-dwell night exchange time of 12±4 hours with a fill volume of at least 2.0L but not more than 2.5L of 2.5% Dextrose were eligible. The randomization for each assignment was stratified for either 2.0 or 2.5L fill volumes. Eligible patients also needed to be requiring a minimum of 4 peritoneal dialysis exchanges per 24 hour period, one of which was a night exchange. Allergy to starch-based polymers, liver disease, and women who were pregnant, lactating or not using acceptable birth control methods were among the exclusion criteria.

Patients continued the same formulation of Dextrose during the other dialysis periods. If a patient was taking Dianeal PD-4, which contains less calcium chloride than PD-2, for the other exchanges, he or she would, if randomized to Icodextrin, get the PD-2 composition of electrolytes for the long-dwell.

Net ultrafiltration was determined by subtracting the inflow amount from the total weight of the long-dwell collection.

The sponsor provided a flowchart of procedures as follows:

VISIT NUMBER	SCREENING PERIOD	BASELINE	TREATMENT PERIOD (DIANEAL® OR ICODEXTRIN) 4 WEEKS	
	-1	0	1	2
WEEK	-2w	0	2w	4w
Intervals	7 d ± 7d	1 d	2w ± 3d	2w ± 3d
Informed Consent	X			
Selection Criteria	X			
Serum hCG ¹	X			
Medical History	X	X		
Physical Exam		X		X
Vital Signs		X	X	X
QoL Evaluation		X		
Lab Analyses ²		X	X ³	X
Chest X-Ray		X		
Concomitant Meds		X	X	X
Adverse Events	X ³	X	X	X
Review Compliance		X	X	X
Randomization		X		
PET		X		
Total Cholesterol		X		X
24 hr. Urine		X		
Ico & met - plasma ⁶		X		X
Ico - dialysate		X		X
12 ± 4 hr Dialysate		X	X	X
HbA _{1c} ⁴		X		X

¹ Women of child-bearing potential.

² To Include biochemistry, hematology with differential and platelets, osmolality.

³ These were considered pre-existing conditions.

⁴ Diabetic patients only.

⁵ Serum BUN and Creatinine only.

⁶ The Icodextrin and metabolites blood sample were drawn at the end of the long dwell, just prior to draining.

	Screen	Baseline	Treatment	
VISIT	-1	0	1	2
Time Period	-1w	0	2w	4w
BLOOD				
Sodium		X		X
Glucose		X		X
Potassium		X		X
Chloride		X		X
HCO ₃		X		X
BUN		X	X	X
Creatinine		X	X	X
Phosphorus		X		X
Calcium		X		X
Total Bilirubin		X		X
SGOT (AST)		X		X
SGPT (ALT)		X		X
Alkaline Phosphatase		X		X
Osmolality		X		X
Albumin		X		X
Amylase		X		X
Hematology		X		X
Total Cholesterol		X		X
Serum hCG ¹	X			
Hb A _{1c} ²		X		X
PET		X		
Icodextrin & met. Analyses ³		X		X
DIALYSATE				
12±4 hr. T. Drain Vol.		X	X	X
12±4 hr. urea nitrogen		X	X	X
12±4 hr. creatinine		X	X	X
Total Icodextrin		X		X
PET		X		
URINE				
24 hr. Collection-RRF		X		

¹ Women of child-bearing potential

² Diabetic patients only

³ The Icodextrin and metabolites blood sample were drawn at the end of the long dwell, just prior to draining

The term PET in this context means peritoneal equilibrium test, and the baseline QoL test was added in the August 1998 amendment after the study had begun for comparison with a follow-up QoL test to be administered to some patients participating in the long term 52 week safety study RD-97-CA-131.

The sponsor provided some baseline characteristics of the 175 randomized patients:

	Control Group		Icodextrin Group		All Patients		p-Value
	N	Percent	N	Percent	N	Percent	
Gender							0.317 *
MALE	26	30.6	34	37.8	60	34.3	
FEMALE	59	69.4	56	62.2	115	65.7	
TOTALS	85	100.0	90	100.0	175	100.0	
Race							0.986 **
CAUCASIAN	47	55.3	48	53.3	95	54.3	
HISPANIC	5	5.9	6	6.7	11	6.3	
ASIAN	3	3.5	2	2.2	5	2.9	
BLACK	27	31.8	30	33.3	57	32.6	
OTHER	3	3.5	4	4.4	7	4.0	
TOTALS	85	100.0	90	100.0	175	100.0	
Primary Renal Diagnosis							0.908 **
DIABETIC NEPHROPATHY	21	24.7	24	26.7	45	25.7	
HYPERTENSIVE NEPHROPATHY	19	22.4	24	26.7	43	24.6	
GLOMERULONEPHRITIS	16	18.8	14	15.6	30	17.1	
POLYCYSTIC KIDNEY DISEASE	3	3.5	2	2.2	5	2.9	
INTERSTITIAL NEPHRITIS	1	1.2	3	3.3	4	2.3	
OBSTRUCTIVE NEPHROPATHY	1	1.2	1	1.1	2	1.1	
AUTOIMMUNE DISEASE	3	3.5	1	1.1	4	2.3	
OTHER	21	24.7	21	23.3	42	24.0	
TOTALS	85	100.0	90	100.0	175	100.0	

@ Analysis of Variance used to test for treatment differences.

* Pearson Chi-Square test used to test for treatment differences.

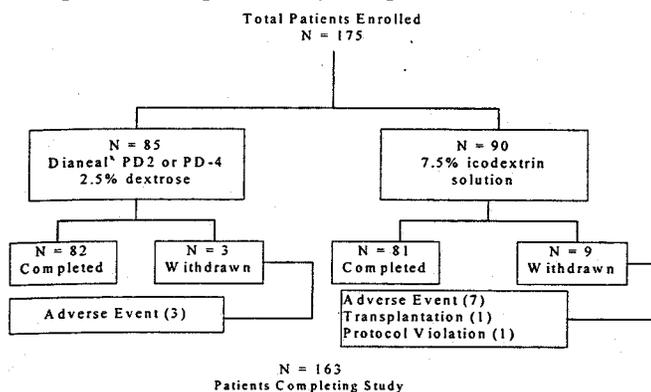
** Fisher Exact test used to test for treatment differences because > 20% of the cells had expected counts < 5.

The groups were also well balanced at baseline for long-dwell glucose concentration and fill volume being used, as well as serum calcium.

Slightly more past episodes of peritonitis were reported for the Icodextrin group (1.2% versus 5.6%, p=0.076), and more months had elapsed from the last exit site infection for the Icodextrin group (mean 14.7 versus 9.1, p=0.062).

59 patients were diabetic (31 Icodextrin patients or 34.4% of the full cohort, and 28 of the Dextrose patients or 32.9%), mostly type II.

Patient disposition was provided by the sponsor as follows:



Details of the reasons for withdrawal were provided:

Treatment Group	Center	Patient	Age/Sex/Race *	Last Study Visit Completed	Last Study Day Completed	Reason for Withdrawal	Description
Control	22	06205	70/F/C	Baseline	15	ADVERSE EXPERIENCE	HOSPITALIZATION FOR MI
	35	15203	50/F/B	Week 2	24	ADVERSE EXPERIENCE	PERITONITIS
	123	29101	78/F/C	Baseline	9	ADVERSE EXPERIENCE	NAUSEA, VOMITING, ANOREXIA, GENERALIZED WEAKNESS, JOINT PAIN, AND SWELLING.
Icodextrin	16	24201	75/M/C	Baseline	12	PROTOCOL VIOLATION	NOT ON 2.5% LONG DWELL FOR 30 DAYS.
		24203	71/M/C	Week 2	36	ADVERSE EXPERIENCE	SEVERE DEHYDRATION AND HYPERKINESIA, PULMONARY EDEMA & BOWEL OBSTRUCTION
	20	21201	47/F/C	Baseline	13	TRANSPLANTATION	
	22	06203	35/F/B	Week 2	50	ADVERSE EXPERIENCE	HOSPITALIZATION FOR APPARENT GIB
	25	22101	51/F/C	Baseline	12	ADVERSE EXPERIENCE	RASH
		23208	52/F/B	Baseline	15	ADVERSE EXPERIENCE	HYPERPIGMENTATION BROWN/RED SKIN SPOTS < 2.0 CM IN SIZE X3 SPOTS. NO C/O ITCHING
	56	23210	60/F/C	Baseline	14	ADVERSE EXPERIENCE	HIVES
		45102	72/F/C	Week 2	29	ADVERSE EXPERIENCE	BLOCKED CATHETER
59	33106	34/F/C	Baseline	8	ADVERSE EXPERIENCE	RASH	

* Age in years / M=Male, F=Female / C=Caucasian, H=Hispanic, A=Asian, B=Black, O=Other

Results were provided for the evaluable population with additional analyses to demonstrate that the ITT results did not materially differ. Compliance was estimated by the number of days the bag was used and was over 80% in both groups. Changes in daytime dialysis prescriptions were similar for the groups. Time of the long-dwell averaged 10.44 hours for control and 10.63 hours for Icodextrin at week 4. Fill volume at that time was 2.2L for each treatment, and drain volumes were 2.6 L and 2.8 L for control and Icodextrin respectively.

EFFICACY

Primary Endpoint-Net UF

At baseline, 2 and 4 week data on dwell start and stop times, volume infused and volume drained were collected on each patient's case report form. For weeks 2 and 4, data from 166 and 163 patients respectively were analyzed by the sponsor to provide the following net UF results:

Treatment Group		(Baseline) Week 0	Week 2	Week 4
Control	No. of Patients	85	82	82
	Mean	328.718	389.793	379.988
	Standard Error	40.997	69.904	37.469
	Minimum	-565.0	-1200.0	-444.0
	Maximum	1400.0	5001.0	1299.0
	Mean Change from Baseline		58.11	44.84
	Min Change from Baseline		-1049.0	-800.0
	Max Change from Baseline		5226.0	995.0
	Mean Pct Change from Baseline *		121.23	56.64
	p-Value for Change from Baseline		0.429	0.179
	Icodextrin	No. of Patients	90	84
Mean		261.922	578.060	605.827
Standard Error		37.514	35.234	31.305
Minimum		-601.0	-300.0	22.0
Maximum		1109.0	1470.0	1376.0
Mean Change from Baseline			300.56	328.17
Min Change from Baseline			-820.0	-668.0
Max Change from Baseline			1568.0	1633.0
Mean Pct Change from Baseline *			356.25	392.75
p-Value for Change from Baseline			<0.001	<0.001
OVERALL ** (From Repeated Measures)		Icodextrin Adjusted Mean Change		294.60
	Control Adjusted Mean Change		70.08	
	Difference (Icodextrin-Control) for Change		224.52	
	Std Error of Difference		50.68	
	Lower 90% Confidence Bound for Difference		140.68	
	Upper 90% Confidence Bound for Difference		308.35	

* Means of individual percent changes from Baseline

** The adjusted mean changes from the repeated measures analysis of covariance, with Baseline value as the covariate, for each treatment group.

A 90% confidence interval was constructed around the difference between Icodextrin and Control.

*** This p-value is from the two-sided test for treatment differences using the repeated measures analysis of covariance.

Mean dwell time was 10.36 hours and mean volume was 2222.55 ml for all patients with a slightly longer dwell time recorded for the Icodextrin patients but no difference in fill volumes between groups.

One patient with an extreme value at week 2 was excluded in an alternative analysis with no change in results. Negative UF values occurred in 13.4% of the control patients versus 0% in the Icodextrin treated patients at 4 weeks ($p < 0.001$).

Nondiabetics had slightly less net UF at 2 weeks versus diabetics, but similar results at 4 weeks. Icodextrin was significantly more effective than control at 2 and 4 weeks in both diabetics and nondiabetics with a somewhat larger net UF benefit for diabetics versus nondiabetics.

Negative UF

Analyses of negative and nonnegative ultrafiltration were carried out at baseline, 2 and 4 week timepoints with the following results:

Visit	Categories	Control Group		Icodextrin Group		All Patients		p-Value
		N	Percent	N	Percent	N	Percent	
Long-Dwell UF (mL)								
BASELINE (Week 0)	Neg UF	16	18.8	18	20.0	34	19.4	0.844 *
	NonNeg UF	69	81.2	72	80.0	141	80.6	
	TOTALS	85	100.0	90	100.0	175	100.0	
WEEK 2	Neg UF	12	14.8	2	2.4	14	8.5	0.004 *
	NonNeg UF	69	85.2	82	97.6	151	91.5	
	TOTALS	81	100.0	84	100.0	165	100.0	
WEEK 4	Neg UF	11	13.4	0	0.0	11	6.7	<0.001 *
	NonNeg UF	71	86.6	81	100.0	152	93.3	
	TOTALS	82	100.0	81	100.0	163	100.0	

* Pearson Chi-Square test used to test for treatment differences.

Secondary Endpoints-Peritoneal Urea Nitrogen and Creatinine Clearance

Blood urea nitrogen and creatinine and dialysate urea nitrogen and creatinine data were collected at baseline, 2 and 4 weeks. Results of peritoneal urea and creatinine clearances (ml/min) were provided as follows:

Variable	Visit	Treatment Group	Baseline@	N	Data					Change from Baseline @					p Betw	
					Mean	Std Err	Min	Median	Max	Mean	Std Err	p W/in	Min	Median		Max
Creatinine Clearance (mL/12 hrs)	Baseline	Control		85	2457.231	63.092	1048.09	2450.26	4201.18							0.733
	(Week 0)	Icodextrin		89	2488.271	65.095	1231.11	2481.72	4333.96							
	Week 2	Control	2472.461	82	2478.179	81.604	926.93	2477.15	6682.97	5.718	82.916	0.945	-1269.18	-35.67	4420.68	<0.001
		Icodextrin	2483.005	84	2943.156	84.749	1572.73	2826.27	6655.63	461.238	76.616	<0.001	-1171.99	464.21	3815.24	
	Week 4	Control	2450.759	81	2523.968	94.904	1049.58	2415.65	7847.31	73.209	92.069	0.429	-1586.18	-19.70	5595.40	0.001
		Icodextrin	2474.555	81	2880.358	73.426	1367.72	2835.26	4715.67	402.287	55.382	<0.001	-943.38	392.25	1908.95	
	Average * (Treatmt)	Control	2461.362	83	2501.684	69.605	1297.51	2489.30	5228.58	40.322	67.898	0.554	-1039.85	-54.39	2976.67	<0.001
Icodextrin		2483.005	84	2902.902	71.387	1584.81	2807.23	4978.38	418.639	58.712	<0.001	-1171.99	439.29	1987.40		
Urea Nitrogen Clearance (mL/12 hrs)	Baseline	Control		85	3002.492	87.319	1352.24	3033.48	5438.46							0.865
	(Week 0)	Icodextrin		90	3022.692	80.026	1572.99	3019.05	4931.37							
	Week 2	Control	3010.738	82	2967.799	94.107	937.14	2884.08	6836.65	-42.939	93.487	0.647	-1773.22	-179.55	4318.05	0.005
		Icodextrin	3034.301	84	3281.972	75.577	1755.74	3243.44	5629.09	247.671	79.131	0.002	-1806.27	288.60	2305.92	
	Week 4	Control	2992.524	82	2964.714	90.330	1349.48	2881.22	5703.75	-27.810	78.235	0.723	-1923.25	-65.44	1852.31	0.004
		Icodextrin	3035.921	80	3260.710	82.168	1510.83	3212.59	5257.34	224.790	64.726	<0.001	-1730.01	228.84	1861.88	
	Average * (Treatmt)	Control	2996.830	83	2962.116	78.987	1414.92	2989.05	4893.52	-34.714	71.318	0.628	-1458.90	-46.20	1885.95	0.001
Icodextrin		3034.301	84	3261.708	72.758	1856.11	3248.68	5226.36	227.407	69.527	0.002	-1806.27	288.78	2083.90		

@ BASELINE is the Week 0 value.

* The average was calculated for each patient during the treatment period. Any patient with data during that time is included.

p W/in= p-value from the within treatment group paired t-test for significant mean change from baseline.

p Betw= Baseline (Wk 0): p-value from analysis of variance testing for significant differences across treatment group means.

Postbaseline (Treatment: Wks 2,4): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

These results support the sponsor's contention that Icodextrin is an effective peritoneal dialysis solution, and provides more net UF and peritoneal urea and creatinine clearance than 2.5% Dextrose for long-dwell dialysis.

SAFETY

175 patients were exposed to either Icodextrin or 2.5% Dextrose. 84.4% of the Icodextrin and 89.4% of the Dextrose patients were treated for more than 27 days. No deaths occurred.

Withdrawals

The reasons for withdrawal were previously presented but is repeated below:

Treatment Group	Center	Patient	Age/Sex/Race *	Last Study Visit Completed	Last Study Day Completed	Reason for Withdrawal	Description
Control	22	06205	70/F/C	Baseline	15	ADVERSE EXPERIENCE	HOSPITALIZATION FOR MI
	35	15203	50/F/B	Week 2	24	ADVERSE EXPERIENCE	PERITONITIS
	123	29101	78/F/C	Baseline	9	ADVERSE EXPERIENCE	NAUSEA, VOMITING, ANOREXIA, GENERALIZED WEAKNESS, JOINT PAIN, AND SWELLING.
Icodextrin	16	24201	75/M/C	Baseline	12	PROTOCOL VIOLATION	NOT ON 2.5% LONG DWELL FOR 30 DAYS.
		24203	71/M/C	Week 2	36	ADVERSE EXPERIENCE	SEVERE DEHYDRATION AND HYPERKINESIA, PULMONARY EDEMA & BOWEL OBSTRUCTION
	20	21201	47/F/C	Baseline	13	TRANSPLANTATION	
	22	06203	35/F/B	Week 2	50	ADVERSE EXPERIENCE	HOSPITALIZATION FOR APPARENT GIB
	25	22101	51/F/C	Baseline	12	ADVERSE EXPERIENCE	RASH
	50	23208	52/F/B	Baseline	15	ADVERSE EXPERIENCE	HYPERPIGMENTATION BROWN/RED SKIN SPOTS < 2.0 CM IN SIZE X3 SPOTS. NO C/O ITCHING
		23210	60/F/C	Baseline	14	ADVERSE EXPERIENCE	HIVES
	56	45102	72/F/C	Week 2	29	ADVERSE EXPERIENCE	BLOCKED CATHETER
	59	33106	34/F/C	Baseline	8	ADVERSE EXPERIENCE	RASH

* Age in years / M=Male, F=Female / C=Caucasian, H=Hispanic, A=Asian, B=Black, O=Other

Serious Adverse Reactions

18 patients (9-Icodextrin, 9-Dextrose) reported serious adverse events with 7 Icodextrin and 8 Dextrose patients being hospitalized. The following list provides a brief primary problem description for each case.

Icodextrin	2.5% Dextrose
Confusion, hypercalcemia, Rocaltretol dc'd	Chest pain, anterior MI
Unresponsive, seizures, bleeding	Abd. pain, nausea and vomiting, Kleb. in dialysate
Nausea and vomiting, bleeding	Flank pain, actinobacter in effluent
Elective renal transplant	Peritonitis
Chest pain	Peritonitis
Tremor, jerky movements, confusion, had Reglan	Peritonitis
Chest pain, CAD	Peritonitis
Pericarditis	Syncope, overuse of 2.5% Dextrose to lose weight
Blocked catheter	Peritonitis

Peritonitis seems to be more frequent as a cause of serious adverse events in the control group, but as noted for all adverse events whether serious or not, 13 or 15% was reported for the Dextrose group compared to 10 or 11% for the Icodextrin group.

Other Adverse Reactions

135 patients reported adverse reactions; 77 Icodextrin (85.6%) versus 58 control (68.2%), p=0.006. Headache, rash and exfoliative dermatitis were more frequently reported in the Icodextrin group. The sponsor notes that rash and exfoliative dermatitis have been ascribed to the use of Icodextrin in the literature.

No difference between cohorts in the incidence of edema during treatment was noted.

Laboratory Findings

Significant changes from baseline values in each group and between groups were noted in the sponsor's chart:

Lab Assay	Visit	Treatment Group	Baseline @	Data		Change from Baseline @		p Betw
			Mean	N	Mean	Mean	p W/in	
SODIUM (MMOL/L)	Week 4	Control	137.988	82	138.061	0.073	0.860	<0.001
		Icodextrin	137.543	81	134.852	-2.691	<0.001	
CHLORIDE (MMOL/L)	Week 4	Control	95.317	82	96.134	0.817	0.031	<0.001
		Icodextrin	95.049	81	93.494	-1.556	<0.001	
CHOLESTEROL (MMOL/L)	Week 4	Control	5.481	82	5.435	-0.046	0.519	0.004
		Icodextrin	5.187	81	4.905	-0.282	<0.001	
AST (SGOT) (U/L)	Week 4	Control	20.500	82	19.951	-0.549	0.359	0.002
		Icodextrin	20.175	81	16.827	-3.313	<0.001	
AMYLASE (U/L)	Week 4	Control	100.695	82	98.012	-2.683	0.307	<0.001
		Icodextrin	103.086	81	16.136	-86.951	<0.001	
ALK PHOS (U/L)	Week 4	Control	87.585	82	84.305	-3.280	0.075	<0.001
		Icodextrin	99.284	81	113.346	14.062	<0.001	

@ BASELINE is the Week 0 value.

p W/in= p-value from the within treatment group paired t-test for significant mean change from baseline.

p Betw= Baseline (Week 0): p-value from analysis of variance testing for significant differences across treatment group means.

Post-baseline (Treatment: Wks 2,4): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

The sponsor claims that the decrease in sodium and chloride is dilutional due to the osmotic effect of Icodextrin and metabolites in the blood that drew water from the intracellular to intravascular compartment. While the slight reduction in cholesterol for the Icodextrin treated patients had been previously reported, it was not thought to be of clinical significance nor is a mechanism for this effect suggested.

The slight decline in AST had not been previously reported had not been previously seen, but was not thought to be of clinical significance and the AST values were all within the normal range.

The decline in serum amylase was ascribed to assay interference, and was previously reported as due to competition by Icodextrin for the substrate used in the assay.

The increase in serum alkaline phosphatase had been previously reported in the PRO-RENAL study, was not associated with changes in other liver enzymes per the sponsor, and was not explained by assay interference. No explanation was proposed by the sponsor.

Another significant shift from baseline to either higher or lower levels was found in the platelet counts for the Icodextrin group. The shifts however were modest and not to levels of clinical concern.

There were changes from baseline glucose in both cohorts mainly from high to normal with no significant difference between cohorts. HgA1C remained normal for both cohorts.

Finally it should be noted that some patients completing the study entered the long-term safety study, RD-97-CA-131.

2. RD-97-CA-131: This was a 52 week randomized, double-blind prospective safety study in 287 ESRD patients undergoing CAPD or APD. The study began on 4/1/98 and ended on 3/17/00. The original protocol was amended twice after study initiation. On 8/13/98 the protocol was amended to increase enrollment to allow inclusion of 60 patients from a European study that was never initiated, and on 1/29/99 to increase enrollment by 75 patients to include patients from study RD-97-CA-130 on the same assignment as designated in that study. The products involved were the same as described above for study RD-97-CA-130.

The primary endpoints were safety endpoints including mortality rates, changes in membrane transport characteristics, adverse reactions, laboratory abnormalities, clinical signs such as edema. The protocol specified reasons for removal of patients from therapy or assessment. These included withdrawal due to adverse event, protocol deviation, transplantation, transfer to hemodialysis and death. For patients terminating prematurely follow-up evaluation was to be completed no more than two weeks following the last dose administered.

No efficacy data was collected, but QoL questionnaires (KDQoL and SF-35) at baseline and at 13, 26, 39 and 52 week timepoints were added and evaluated for those who completed these at baseline and week 52. The sizing of the study was based on mortality estimates for the two groups with the hypothesis being that the mortality rates would be comparable. Mortality rates were to be calculated by determining number of deaths of any patient during the treatment or follow-up periods of the study, and comparing the rates for each group. In the 1/29/99 amendment a secondary analysis of mortality was added which was to do a survival analysis of time to death using a logrank test.

The schedule of study procedures was:

VISIT NUMBER WEEK	SCREENING PERIOD	BASELINE	TREATMENT PERIOD (DIANEAL® OR ICODEXTRIN) 52 WEEKS			
	-1	0	1	2	3	4
	-2	0	13	26	39	52
Intervals	7d ± 7d	1d	13w±1w	13w±1w	13w±1w	13w± 1w
Informed Consent	X					
Selection Criteria	X					
Serum hCG ¹	X					
Medical History	X	X				
Physical Exam		X				X
Vital Signs		X	X	X	X	X
KDQoL Evaluation		X	X	X	X	X
Lab Analyses ²		X	X	X	X	X
Chest X-ray		X				X
Concomitant Meds		X	X	X	X	X
Adverse Events	X ³	X	X	X	X	X
Review Compliance		X	X	X	X	X
Randomization		X				
PET		X		X ⁴		X ⁴
24-hour Urine Collection		X		X		X
Plasma icodextrin and metabolites ⁶		X	X	X	X	X
Hb A _{1c} ⁵		X	X	X	X	X

¹ Women of childbearing potential.

² To include biochemistry, hematology with differential and platelets, and osmolality.

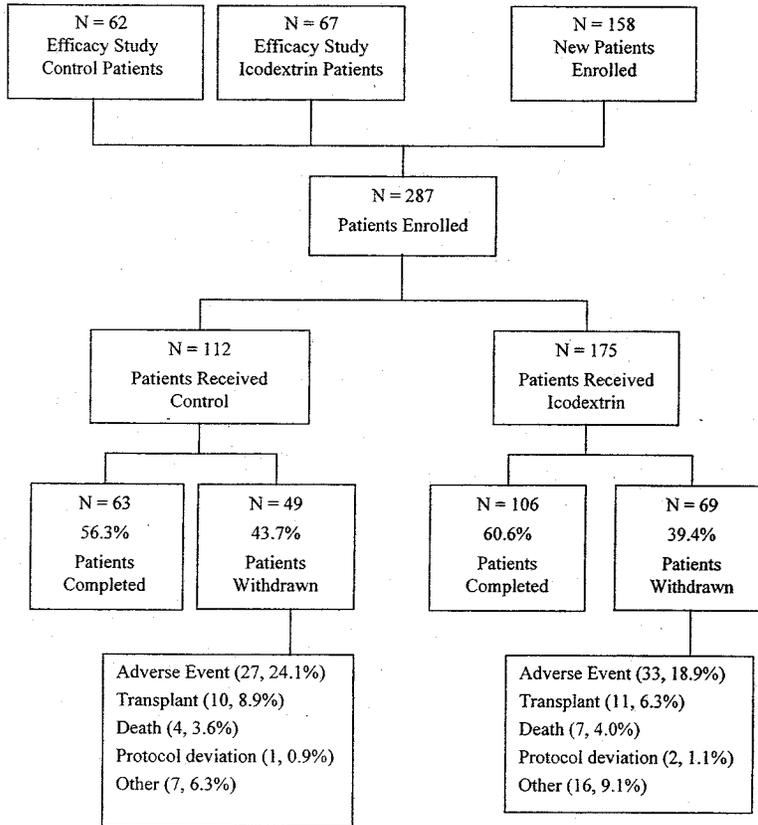
³ These will be considered pre-existing conditions.

⁴ The long dwell preceding the PET at the Week 26 and Week 52 Visits will be standardized to Dianeal® for all patients. The sample for icodextrin and metabolites that correlates with these visits must be drawn at the end of any investigational product long dwell in the week preceding the visit.

⁵ Diabetic patients, only.

⁶ The icodextrin metabolites blood sample must be drawn at the end of the long dwell just prior to draining

158 new patients were randomized and enrolled. 129 patients from other studies as described above were included in the study but not rerandomized. The disposition of subjects in the study was:



Baseline demographics for the 287 patients entered into the study were:

	Control Group		Icodextrin Group		All Patients		p-Value
AGE							0.337 [®]
N	112		175		287		
Mean ± SE	55.1 ± 1.23		53.5 ± 1.05		54.1 ± 0.80		
Min – Max	25 – 86		22 – 83		22 – 86		
	N	Percent	N	Percent	N	Percent	
GENDER							0.160 [*]
Male	50	44.6	93	53.1	143	49.8	
Female	62	55.4	82	46.9	144	50.2	
Totals	112	100.0	175	100.0	287	100.0	
RACE							0.976 ^{**}
Caucasian	70	62.5	110	62.9	180	62.7	
Hispanic	5	4.5	7	4.0	12	4.2	
Asian	4	3.6	9	5.1	13	4.5	
Black	31	27.7	46	26.3	77	26.8	
Other	2	1.8	3	1.7	5	1.7	
Totals	112	100.0	175	100.0	287	100.0	

[®] Analysis of Variance used to test for treatment differences.

^{*} Pearson Chi-Square test used to test for treatment differences.

^{**} Fisher Exact test used to test for treatment differences because >20% of the cells had expected counts <5.

Primary renal diagnoses were balanced for the two cohorts:

Primary Renal Diagnosis	Control Group		Icodextrin Group		All Patients		p-Value
	N	%	N	%	N	%	
Diabetic Nephropathy	39	34.8	53	30.3	92	32.1	0.660 ^{**}
Hypertensive Nephropathy	24	21.4	40	22.9	64	22.3	
Glomerulonephritis	20	17.9	27	15.4	47	16.4	
Polycystic Kidney Disease	3	2.7	7	4.0	10	3.5	
Interstitial Nephritis	0	0.0	6	3.4	6	2.1	
Obstructive Nephropathy	1	0.9	2	1.1	3	1.0	
Autoimmune Disease	4	3.6	5	2.9	9	3.1	
Other	21	18.8	35	20.0	56	19.5	
TOTALS	112	100.0	175	100.0	287	100.0	

^{**} Fisher Exact test used to test for treatment differences because >20% of the cells had expected counts of <5.

References: Table 14.1-1; Appendix 16.2.4.

As per the sponsor, the number of patients remaining in the study at the scheduled visits were:

Visit	Treatment Group		Total N
	Control	Icodextrin	
	N	N	
Baseline	112	175	287
Week 2 Visit	103	147	250
Week 4 Visit	103	147	250
Week 13 Visit	94	143	237
Week 26 Visit	83	130	213
Week 39 Visit	70	111	181
Week 52 Visit	62	104	166

References: Table 14.1-12; Appendix 16.4.

Exposure to study drug calculated from first dose to discharge or time in study was:

Time in Study	Control Group		Icodextrin Group		All Patients	
	N	Percent	N	Percent	N	Percent
< 2 weeks	1	0.9	5	2.9	6	2.1
> 2 - < 4 weeks	2	1.8	7	4.0	9	3.1
> 4 weeks - < 3 months	13	11.6	18	10.3	31	10.8
> 3 - < 6 months	12	10.7	16	9.1	28	9.8
> 6 - < 9 months	13	11.6	18	10.3	31	10.8
> 9 - < 12 months	10	8.9	10	5.7	20	7.0
12 months	61	54.5	101	57.7	162	56.4

References: Table 14.3.1; Appendix 16.4.

Mortality

The protocol called for a 30 day follow-up post-withdrawal or completion, In the original submission, it was stated that 5 patients in the control group and 13 in the Icodextrin group had died. This count was based on deaths occurring during the study or 30 days following the study or withdrawal. The sponsor's initial listing and brief synopsis of each patient who died follows:

Pt. #	Age/Sex/Race*	Days in Study	Adverse Events with Outcome "Death"***
CONTROL (n=5)			
18102	59 / F / C	160	Cellulitis, cardiac arrest, hypoalbuminemia, wheezing
21205	66 / M / C	223	Cardiac arrest, cold feet, anorexia, constipation, decreased creatinine clearance, peripheral edema, bone pain, dyspnea, pruritus, skin disorder
22102	45 / F / C	303	Back pain, bowel obstruction, stomach ulcer, aspiration pneumonia, nervousness, hypoproteinemia, hypocholesterolemia, hypokalemia, hyponatremia
35101	58 / F / C	113	MI, hypoproteinemia
40301†	63 / F / C	367	CHF, heart failure, pneumonia, hypothyroid, skin ulcer
ICODEXTRIN (n=13)			
06102	46 / M / B	78	Retroperitoneal hemorrhage, syncope, electrolyte abnormalities, uremia, ileus, abnormal thinking, peritonitis, vascular disease, hypotension, cardiovascular disease, anemia, increased alkaline phosphatase, decreased weight, polycystic kidney disease, edema, increased AST
11601†	46 / M / C	133	Gangrene, sepsis, heart arrest, anemia, hypoproteinemia, neuropathy
18106	47 / F / B	148	Diabetic coma, heart arrest, cardiac murmur
22106†	59 / M / C	226	Sepsis, monilia, coronary artery disease, calcium disorder, hyperphosphatemia, hypocalcemia, dehydration, increased urea nitrogen, rash, cardiovascular disease, acidosis
22202	48 / M / C	324	Peritonitis, MI, stool abnormality, depression, insomnia, high serum osmolality, hyperphosphatemia, increased urea nitrogen, hypoproteinemia
26503†	63 / M / A	15	Sepsis
27102	65 / M / B	169	Heart arrest
30302	77 / F / C	164	CVA, peritonitis, anemia
30501†	68 / M / C	108	Heart arrest, artery occlusion, genital edema
35401†	82 / M / C	206	Pneumonia, CVA, diabetes mellitus
42302	63 / F / C	36	Hemorrhagic gum, shock, MI, angina, intestinal necrosis, pneumonia, peripheral vascular disease, bursitis, peripheral neuritis, retinal disease, fibrocystic breasts
45401†	49 / M / C	15	Heart arrest, peritonitis, anemia, rash, stool abnormality, increased alkaline phosphatase, alopecia
62501	60 / F / B	49	Death secondary to MI

F=female, M=male, B=black, C=Caucasian, A=Asian. ***CABG=coronary artery bypass graft, CHF=congestive heart failure, CVA=cerebrovascular accident, MI=myocardial infarction. †Patients who expired during the follow-up period.

10 of the 13 deaths on Icodextrin died before 6 months, while 2 of the 5 control patients died in that timeframe.

Of the Icodextrin patients who died 8 (62%) were diabetics compared to 1 (20%) in the Dextrose group. Alkaline phosphatase elevations were associated with transaminase elevations in 3 of the Icodextrin patients who died. History of hypertension and cardiovascular disease was frequently present in both cohorts. 5 Icodextrin patients who died had an episode of hypotension documented compared to 1 in the Dextrose group, however visits for evaluation in this study were infrequent.

The results for this initial mortality result were:

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	112	5	4.5	395	395	N/A	385.8 #	5.21	377.3	394.4	0.336
Icodextrin	175	13	7.4	N/A	N/A	N/A	345.2 #	5.40	336.3	354.1	
TOTALS	287	18	6.3	N/A	N/A	N/A	378.8 #	4.14	372.0	385.6	

* p-Value is from the LogRank test comparing the survival curves between groups.
 # The mean and standard error were underestimated because the largest observation was censored.
 N/A: there were not enough deaths to estimate this quartile.

Mortality Rates (per Month and per Year) Based on Poisson Estimation

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1027.3	5	0.005	0.000	0.120	0.06	0.00	1.44
Icodextrin	175	1600.3	13	0.008	0.000	0.156	0.10	0.00	1.88

90% Confidence Intervals are presented as specified in the protocol to estimate whether the two drugs had similar mortality risk associated with their use. Based on the initial results, it could not be concluded that the risk was similar, although the numerical difference was not statistically significant. At the October 19, 2000 CRDAC meeting it was suggested that for the mortality analysis follow-up of all randomized patients should be done for the 52 week duration of the trial plus 30 days. The sponsor therefore amended the protocol to provide a 13 month follow-up for all patients. In the March 20, 2001 submission the sponsor provided final mortality results which included follow-up results on all but 3 of the randomized subjects. In this new tally it was noted that 16 patients had died (9-Icodextrin, 7-Control) in addition to the 18 already reported. A brief narrative for each of the new patients reported dead follows. A star following the patient number indicates that the death occurred later than 13 months post-enrollment of follow-up.

Patients assigned to Icodextrin:

02401 was a 48 year old female Caucasian with type I diabetes. She entered on 12/14/98 and was withdrawn on 2/3/99 for pericarditis. She died on 6/7/99 from a CVA including intracranial hemorrhage.

19503 was a 50 year old Black male with hypertension who entered on 2/16/99 (BP 90/70). The patient was withdrawn on 4/20/99 due to a rash and itching (BP118/60). The patient died on 11/21/99 of some unspecified cardiac problem.

24204* was a 69 year old male Caucasian with type I diabetes who entered on 9/17/98 with a BP 141/68. On 11/20/98 complaints of hypotension, dizziness and chest pain were noted. The patient withdrew on 4/9/99 due to peritonitis, and died on 1/19/2000 of cardiac arrest. Death occurred after the 13 month post-enrollment period being considered.

24502* was a 62 year old male Caucasian who entered on 8/17/98 and was withdrawn on 9/12/98 due to appendicitis. He died on 7/21/2000 from cardiac arrest.

32301 was a 37 year old female Caucasian with type I diabetes. She entered on 2/16/99, had a myocardial infarction on 4/7/99 and was noted to have a problem with diabetic control on 5/20/99. She withdrew on 6/3/99 for muscle aches, and died on 12/5/99 from diabetes, severe peripheral vascular disease and withdrawal from dialysis.

35301 was a 70 year old female Caucasian with type II diabetes and hypertension. She entered 10/16/98, and withdrew on 1/14/99 after her husband's death. She died 3/20/99 of renal failure.

38102 was an 82 year old male Caucasian with type II diabetes. He entered on 10/27/98 (BP140/70), and was noted to have hypotension on 11/4/98. On 5/10/99 fluid overload was found, and the patient was withdrawn on 5/20/99 for membrane failure. The patient died of ESRD on 7/9/99.

38103 was a 74 year old male Hispanic with hypertension. He entered on 10/27/98 (BP130/80), and developed hypotension and dehydration on 6/22/99. He was withdrawn for a cardiac mass on 7/7/99, and died on 10/25/99 with peripheral vascular disease noted.

61603 was a 66 year old male Caucasian with hypertension. He entered 11/13/98 (BP170/80), and withdrew for joint aches on 1/12/99. He died on 6/20/99 of cardiac arrest.

Patients assigned to control:

01501 was a 50 year old Caucasian female with type I diabetes. She entered on 8/17/98, was withdrawn on 3/5/99 for hypoglycemia, and died on 4/13/99 from unknown cause.

15202 was a 42 year old Black female with type II diabetes. She entered on 7/24/98 and was withdrawn on 8/15/98 for peritonitis. She died on 12/17/98 from unknown cause.

24202* was a 50 year old Black male with hypertension. He entered on 7/29/98 (BP 162/78), and died 12/9/99 of cardiac arrest/arrhythmia.

24501* was a 60 year old Caucasian male with type I diabetes. He entered on 7/31/98, and withdrew on 9/23/98 for peritonitis. He died on 9/10/99 from cardiac arrest.

30601* was a 69 year old Caucasian male with diabetes who entered on 11/16/98 and withdrew on 12/9/98 for unresolved peritonitis. He died on 5/26/00, no cause given.

32401 was a 64 year old Black male who entered on 1/14/99, withdrew on 10/14/99 for peritonitis, and died 1/7/2000 from cardiac arrest.

43403 was a 60 year old male Caucasian with type II diabetes. He entered 3/8/99, withdrew 7/23/99, and died 3/2/2000 from multisystem organ failure.

Although 16 new deaths were reported (7 on control and 9 on Icodextrin), only 11 (4 on control and 7 on Icodextrin) occurred 13 months post-enrollment. Therefore, the sponsor's analysis included 29 deaths: 20 (11.4%) randomized to Icodextrin and 9 (8.0%) to control. With these additional cases, the number of diabetics was 12 (60%) in the Icodextrin mortality group and 4 (44%) in the Dextrose group.

The sponsor provided a variety of analyses.
 Their survival analysis indicating days to death or censoring was:

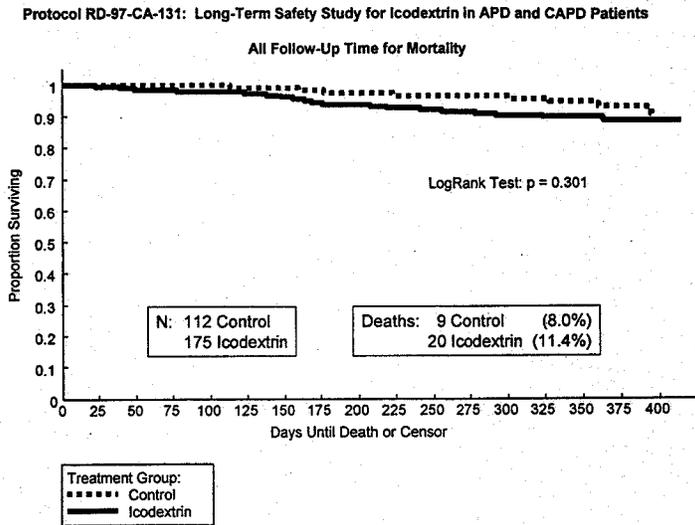


Table 1: Mortality Analysis Including Additional Follow-up Data
 Based on Survival Times in Days -- Survivors Have Censored Times

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 95% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	112	9	8.0	N/A	N/A	N/A	384.8 #	4.40	376.2	393.4	0.301
Icodextrin	175	20	11.4	N/A	N/A	N/A	343.9 #	5.07	333.9	353.8	
TOTALS	287	29	10.1	N/A	N/A	N/A	376.6 #	3.86	369.0	384.1	

* p-Value is from the LogRank test comparing the survival curves between groups.
 # The mean and standard error were underestimated because the largest observation was censored.
 N/A: There were not enough deaths to estimate this quartile.

Mortality rates per-month and per-year with 90% confidence intervals were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1356.1	9	0.007	0.000	0.141	0.08	0.00	1.69
Icodextrin	175	2009.6	20	0.010	0.000	0.174	0.12	0.00	2.09

@ the estimated mean and 90% confidence interval are displayed.

Table 3: Differences Between Mortality Rates (per Month and per Year) Based on Poisson Estimation
 Equivalence of Icodextrin and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin Mean	Control Mean	Difference (Ico - Cntl)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Cntl)	Lower 90%	Upper 90%
0.010	0.007	0.003	0.0031	-0.002	0.008	0.040	-0.022	0.102

Since there was some numerical difference in mortality rates suggesting a possible increased risk with Icodextrin, numerous subgroup analyses were done. These should be considered exploratory, and since the overall result was inconclusive, such further analyses should be considered with more scepticism than usual.

There were 4 prespecified randomized strata: 1) APD/2L, APD/2.5L, CAPD/2L, and CAPD/2/5L. The results for each stratum with 90% confidence intervals follows.

APD MORTALITY

77 patients underwent APD; 41 assigned to Icodextrin and 36 to control. There were 40 males, 37 females with a mean age of 53.5 years. 52 were Caucasian, 19 Black, 4 Asian and 1 Hispanic. 22 had diabetic nephropathy, 17 hypertensive nephropathy, 12 glomerulonephritis, 3 autoimmune disease and 23 other. 22 were Canadians. The demographics were well balanced between treatments.

Of these 77 patients, 50 completed the study, 5 withdrew for transplantation, 13 for an adverse experience, 1 for a protocol violation, 4 for other reasons, and 4 died in the per-protocol analysis.

In most respects the APD cohort behaved similarly to the CAPD cohort, though the sponsor notes that there was less evidence of any favorable trend in weight maintenance for Icodextrin. Also, comparing the Icodextrin CAPD group with the APD group, larger decreases in blood glucose levels in the APD Icodextrin group were noted.

The mortality rates with 90% CIs were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	36	428.8	4	0.009	0.000	0.168	0.11	0.00	2.02
Icodextrin	41	469.4	5	0.011	0.000	0.180	0.13	0.00	2.17

@ the estimated mean and 90% confidence interval are displayed.

For the APD/2L stratum;

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	23	272.5	3	0.011	0.000	0.184	0.13	0.00	2.20
Icodextrin	30	339.5	4	0.012	0.000	0.190	0.14	0.00	2.28

@ the estimated mean and 90% confidence interval are displayed.

For the APD/2.5L stratum:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	13	156.3	1	0.006	0.000	0.138	0.08	0.00	1.66
Icodextrin	11	129.9	1	0.008	0.000	0.152	0.09	0.00	1.82

@ the estimated mean and 90% confidence interval are displayed.

CAPD MORTALITY

210 patients underwent CAPD. 76 were assigned to Dextrose for the long-dwell, 134 were assigned to Icodextrin. The mortality rates for this cohort using the per-advisory committee follow-up database were.

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	76	927.3	5	0.005	0.000	0.126	0.06	0.00	1.51
Icodextrin	134	1540.2	15	0.010	0.000	0.172	0.12	0.00	2.06

@ the estimated mean and 90% confidence interval are displayed.

For the CAPD/2L stratum, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	34	413.0	2	0.005	0.000	0.119	0.06	0.00	1.43
Icodextrin	75	862.9	9	0.010	0.000	0.178	0.13	0.00	2.14

@ the estimated mean and 90% confidence interval are displayed.

For the CAPD/2.5L stratum, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	42	514.4	3	0.006	0.000	0.131	0.07	0.00	1.58
Icodextrin	59	677.3	6	0.009	0.000	0.164	0.11	0.00	1.96

@ the estimated mean and 90% confidence interval are displayed.

Some patients entered from study 130 They continued on the assignment they were randomized to in that study and had successfully completed the 4 week treatment period of that study. To explore the mortality results of that cohort versus the newly randomized patients who entered study 131, the following analyses were done.

STUDY 130 PATIENTS

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	62	733.9	5	0.007	0.000	0.143	0.08	0.00	1.71
Icodextrin	67	777.2	7	0.009	0.000	0.165	0.11	0.00	1.98

@ the estimated mean and 90% confidence interval are displayed.

STUDY 131 PATIENTS

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	50	622.2	4	0.006	0.000	0.138	0.08	0.00	1.66
Icodextrin	108	1232.4	13	0.011	0.000	0.180	0.13	0.00	2.15

@ the estimated mean and 90% confidence interval are displayed.

The mortality rate for the control patients was 8% for each cohort. For those taking Icodextrin the mortality rate was 10.5% for study 130 patients, and 12% for study 131 patients. The difference is not large enough to suggest that results would have been significantly different had all new patients entered study 131.

PD-2 and PD-4 MORTALITY

One requested analysis was to compare mortality in those taking PD-2 electrolytes versus PD-4 electrolytes in the other exchanges. As previously stated, PD-4 has slightly less calcium chloride than PD-2, and might be selected for a patient who had elevated serum calcium. Since Icodextrin is supplied with PD-2 electrolytes only, during the long-dwell that patient would get the slightly greater amount of calcium chloride in that formulation.

The number taking PD-2 or PD-4 at entry was:

	U.S.		Canada	
	Control N (%)	Icodextrin N (%)	Control N (%)	Icodextrin N (%)
PD-2	42 (50%)	58 (45%)	0 (0%)	0 (0%)
PD-4	42 (50%)	71 (55%)	28 (38%)	46 (62%)

The mortality rate for those taking PD-2 at baseline was:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	42	502.6	4	0.008	0.000	0.155	0.10	0.00	1.86
Icodextrin	58	673.9	4	0.006	0.000	0.133	0.07	0.00	1.59

@ the estimated mean and 90% confidence interval are displayed.

For those taking PD-4 at baseline the mortality rates were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	70	853.5	5	0.006	0.000	0.132	0.07	0.00	1.58
Icodextrin	117	1335.7	16	0.012	0.000	0.192	0.14	0.00	2.30

@ the estimated mean and 90% confidence interval are displayed.

For the Icodextrin patients taking PD-2 at baseline the mortality rate was 6.9% versus 13.7% in those taking PD-4.

CANADIAN AND US MORTALITY

Since Canadians took only PD-4 at baseline a tabulation of their mortality rate was requested:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	28	338.1	2	0.006	0.000	0.132	0.07	0.00	1.59
Icodextrin	46	527.1	8	0.015	0.000	0.218	0.18	0.00	2.61

@ the estimated mean and 90% confidence interval are displayed.

Their mortality rate was 17.3% on Icodextrin. Control mortality rate here was 7.1%.

The US results were also calculated:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	84	1018.0	7	0.007	0.000	0.143	0.08	0.00	1.72
Icodextrin	129	1482.5	12	0.008	0.000	0.156	0.10	0.00	1.87

@ the estimated mean and 90% confidence interval are displayed.

DIABETIC MORTALITY

Since many of those who died were diabetic, a comparison of mortality rates for diabetes and no diabetes at baseline was requested. For diabetics these results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	51	625.9	4	0.006	0.000	0.138	0.08	0.00	1.65
Icodextrin	68	754.4	10	0.013	0.000	0.203	0.16	0.00	2.43

@ the estimated mean and 90% confidence interval are displayed.

For nondiabetics results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	61	730.2	5	0.007	0.000	0.143	0.08	0.00	1.72
Icodextrin	107	1255.2	10	0.008	0.000	0.155	0.10	0.00	1.86

@ the estimated mean and 90% confidence interval are displayed.

The mortality rate for those with diabetes at baseline and assigned to Icodextrin was 14.7% compared to 9.3% in nondiabetics assigned to Icodextrin.

None of these subgroup results are significant, and any hypotheses that might be considered would be speculative, needing prospective testing, at best.

QUALITY OF LIFE

The kidney disease quality of life (KDQoL) and short form 36 (SF-36) questionnaires were used. The KDQoL form contained a 35 symptom/problem list. SF-36 had 36 questions about the patient's general health covering mental and physical health. The protocol did not specify how these results were to be interpreted.

The KDQoL results for the 66 patients (41-Icodextrin and 25-Dextrose) who completed baseline and 52 week questionnaires as well as for 138 patients (63-Icodextrin, 75-Dextrose) for whom there was some data. There were no significant differences in overall score between treatments for either the KDQoL or SF-36 instruments for either cohort. Nor were changes from baseline to week 52 for individual questions such as soreness of muscles, trouble breathing significantly different between treatments.

A technical report from the Ovation Research group of Highland Park, Illinois analyzed the data for clinically significant differences. They state "The determination of a clinically meaningful change score (also referred to as a minimally important difference) is a relatively recent pursuit by HRQOL scientists, and, as such, more research will be required before validated rules can be established for all HRQOL measures."

They note that guidelines from the SF-36 developer suggest that a 5-10 point change in any subscale is clinically meaningful, and using a 3/5 point difference between groups they provided the following results from the KDQoL data:

<i>Treatment Advantage¹ for Problem/Symptom Items</i>	
Icodextrin	Dianeal
m. Dry skin	e. Ache in bones
u. Lack of strength	h. Headaches
x. Numbness in hands or feet	n. Trouble getting your breath
aa. Trouble concentrating or thinking	o. Shortness of breath
	s. Dry mouth
	t. Excessive thirst
	ee. Trouble sleeping

From the SF-36 data they provided the following:

Domains	Within Group		Between-Group
	Control	Icodextrin	Differences
Physical Functioning	-7.2	-6.5	0.7
Role-Physical	-20.8	-6.0	14.8 *
Bodily Pain	-3.3	2.4	5.7 *
General Health	-6.5	-1.5	5.0 *
Vitality	-0.2	-5.5	-5.3 **
Social Functioning	-4.5	-4.9	-0.4
Role-Emotional	-7.2	-2.2	5.0 *
Mental Health	0.4	-0.2	-0.6
Physical Component Summary	-4.1	-1.5	2.6
Mental Component Summary	0.0	-0.4	-0.4

*Clinically meaningful difference favoring Icodextrin Group.

**Clinically meaningful difference favoring Control Group.

Additionally, a health transition frequency summary based on responses to the question “compared to one year ago, how would you rate your health in general now?” was provided for those with baseline and week 52 responses.

Response	Control Group (n=25)		Icodextrin Group (n=40)		p-Value**
	n	%	n	%	
Much better now than one year ago	1	4.0%	12	30.0%	0.030
Somewhat better now than one year ago	7	28.0%	6	15.0%	
About the same as one year ago	13	52.0%	19	47.5%	
Somewhat worse now than one year ago	4	16.0%	2	5.0%	
Much worse now than one year ago	0	0.0%	1	2.5%	

*KDQoL Question-3: Compared to 1 year ago, how would you rate your health in general now?

**Chi-Square and, when appropriate, Fisher's Exact test. Reference: Appendix 16.2.9.

It is not clear why 40 Icodextrin patients rather than 41 are included in this analysis, but whatever nominal significance was claimed in this analysis was not present at weeks 13, 26 and 39.

ADVERSE REACTIONS

Serious adverse reactions were noted in 86 (51.2%) Icodextrin and 57 (51.4%) Dextrose patients. Hospitalization was the reason for classifying these events as serious in over 80% of cases with lesser percentages due to death or the life-threatening nature of the event. Hospitalization rates were similar for the two groups (17.1% for Icodextrin patients and 21.4% for the Dextrose patients). Events such as peritonitis, nausea and vomiting, MI were frequently noted in these patients as they were for other adverse reactions reported in this study.

60 patients (18.9% Icodextrin patients; 24.1% Dextrose patients) discontinued the study for adverse events. Most of these withdrawals were due to peritonitis, infection, dehydration, 5 Icodextrin patients withdrew for rash compared to none in the Dextrose group. Rash was reported 13 times in the Dextrose group versus 37 times in the Icodextrin group.

The frequencies of adverse reactions in the treatment and follow-up periods of the study was:

COSTART Body System	Control Group				Icodextrin Group			
	Mild	Mod	Sev	Total	Mild	Mod	Sev	Total
BODY GENERAL	148	137	30	315	283	207	41	531
CARDIOVASCULAR	42	60	20	122	64	89	27	180
DIGESTIVE	68	71	7	146	133	88	15	236
ENDO	12	2	0	14	7	7	0	14
HEMATOLOGIC AND LYMPHATIC	28	27	2	57	55	34	7	96
METABOLIC AND NUTRITION	141	112	17	270	213	116	13	342
MUSCULOSKELETAL	21	22	1	44	39	24	8	71
NERVOUS	40	36	1	77	54	51	3	108
RESPIRATORY	64	33	2	99	117	39	7	163
SKIN	55	30	3	88	68	47	3	118
SPECIAL SENSES	22	7	1	30	27	12	1	40
UROGENITAL	18	20	2	40	31	21	4	56
--- TOTALS ---	659	557	86	1302	1091	735	129	1955

All Adverse Events per patient after Baseline are counted.
Mod= Moderate, Sev= Severe

While overall the percentages in each costart category were similar, for specific terms where there was at least a 5% difference in incidence between groups, there were numerical differences that in most cases favored Icodextrin.

COSTART BODY SYSTEM	Control Group N=112		Icodextrin Group N=175	
	N	Percent	N	Percent
BODY GENERAL				
Exit Site Infection	24	21.4	28	16.0
Headache	9	8.0	25	14.3
Allergic Reaction	9	8.0	5	2.9
CARDIOVASCULAR				
Hypotension	27	24.1	25	14.3
DIGESTIVE				
Nausea	9	8.0	25	14.3
METABOLIC AND NUTRITIONAL				
Hypoproteinemia	20	17.9	22	12.6
Hypokalemia	26	23.2	21	12.0
Edema Peripheral	20	17.9	11	6.3
RESPIRATORY				
Dyspnea	17	15.2	13	7.4
SKIN				
Rash	13	11.6	33	18.9
Skin Disorder	15	13.4	9	5.1

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin Group.

Laboratory Findings

The following chart provides the sponsor's assessment of significant changes from baseline in laboratory values over time. The week 4 baseline values include the data of patients from RD-97-CA-130 who were rolled over into study RD-97-CA-131.

Lab Assay	Visit	Treatment Group	Baseline Mean [®]	Data		Change from Baseline		p Betw
				N	Mean	Mean	p W/in	
Sodium (mmol/L)	Week 4	Control	138.000	62	138.161	0.161	0.752	<0.001
		Icodextrin	137.642	67	134.910	-2.731	<0.001	
	Week 13	Control	138.457	94	138.436	-0.021	0.957	<0.001
		Icodextrin	138.224	143	135.748	-2.476	<0.001	
	Week 26	Control	138.321	81	137.963	-0.358	0.475	<0.001
		Icodextrin	138.313	128	135.148	-3.164	<0.001	
	Week 39	Control	138.386	70	137.643	-0.743	0.191	<0.001
		Icodextrin	138.396	111	134.604	-3.793	<0.001	
Week 52	Control	138.349	63	138.381	0.032	0.957	<0.001	
	Icodextrin	138.433	104	135.596	-2.837	<0.001		
Chloride (mmol/L)	Week 4	Control	95.097	62	95.774	0.677	0.149	<0.001
		Icodextrin	95.299	67	93.493	-1.806	<0.001	
	Week 13	Control	95.702	94	96.351	0.649	0.115	<0.001
		Icodextrin	95.944	143	94.021	-1.923	<0.001	
	Week 26	Control	95.704	81	96.086	0.383	0.420	<0.001
		Icodextrin	96.117	128	94.133	-1.984	<0.001	
	Week 39	Control	95.643	70	96.314	0.671	0.198	<0.001
		Icodextrin	95.964	111	93.991	-1.973	<0.001	
	Week 52	Control	95.619	63	96.714	1.095	0.070	<0.001
		Icodextrin	95.923	104	94.798	-1.125	0.007	

Lab Assay	Visit	Treatment Group	Baseline [®] Mean	Data		Change from Baseline		p Betw	
				N	Mean	Mean	p W/in		
AST (SGOT) (U/L)	Week 4	Control	21.145	62	20.919	-0.226	0.763	0.009	
		Icodextrin	19.773	67	17.030	-2.697	0.004		
	Week 26	Control	21.901	81	22.000	0.099	0.936	0.006	
		Icodextrin	20.039	128	18.414	-1.575	0.073		
	Week 39	Control	21.814	70	22.771	0.957	0.567	0.008	
		Icodextrin	19.555	111	18.423	-1.073	0.209		
Amylase (U/L)	Week 4	Control	96.645	62	93.435	-3.210	0.298	<0.001	
		Icodextrin	100.254	67	15.522	-84.731	<0.001		
	Week 13	Control	95.468	94	91.351	-4.117	0.194	<0.001	
		Icodextrin	98.986	143	16.902	-82.084	<0.001		
	Week 26	Control	95.630	81	87.358	-8.272	0.029	<0.001	
		Icodextrin	99.664	128	17.305	-82.359	<0.001		
	Week 39	Control	96.957	70	90.686	-6.271	0.035	<0.001	
		Icodextrin	98.342	111	13.793	-84.550	<0.001		
	Week 52	Control	97.397	63	93.079	-4.317	0.262	<0.001	
		Icodextrin	101.317	104	14.288	-87.029	<0.001		
	Osmolality (mOsm/kg)	Week 39	Control	315.971	70	311.257	-4.714	0.023	0.007
			Icodextrin	315.945	110	316.882	1.009	0.557	
Alkaline Phosphatase (U/L)	Week 4	Control	88.532	62	85.452	-3.081	0.146	<0.001	
		Icodextrin	87.403	67	102.343	14.940	<0.001		
	Week 13	Control	92.817	94	91.266	-1.183	0.826	0.002	
		Icodextrin	86.150	142	100.923	15.179	<0.001		
	Week 26	Control	93.913	81	90.704	-2.788	0.630	0.002	
		Icodextrin	85.683	128	101.164	15.833	<0.001		

[®] Baseline is the Week 0 value. Baseline means are calculated from patients with observations at each respective visit.
pW/in = p-Value from the within treatment group paired t-test for significant mean change from Baseline.
pBetw = Baseline (Week 0): p-Value from analysis of variance testing for significant differences across treatment group means (p<0.01). Post Baseline (Treatment Weeks 13, 26, 39, 52): p-Value from analysis of covariance testing for significant differences across treatment groups for mean changes (p<0.01).

As adverse events hyponatremia or hypochloremia were reported for 6.9% of the Icodextrin patients and 4.5% of the Dextrose patients. Increased alkaline phosphatase was reported in 6.9% and 5.4% of the Icodextrin and Dextrose groups respectively. One Icodextrin patient had cholestatic jaundice associated with the elevated alkaline phosphatase. Two Icodextrin patients who died were reported to have had elevated alkaline phosphatase. No significant differences between treatments in platelet shifts were reported in this study, but slight reductions in cholesterol at several timepoints were noted for the Icodextrin group. The sponsor postulated that the increases in plasma osmolality were due to low molecular weight metabolites of Icodextrin.

While there was no significant difference in serum calcium levels between treatments over time in either this study or study 130, one could not rule out a detrimental effect in certain patients such as those with hypercalcemia. A review of the case report forms for those assigned to Icodextrin who had been on the low calcium PD4 solution before admission did not reveal data to suggest a problem due to use of the PD 2 solution for the long-dwell.

PET and MTAC

Results for the Peritoneal Equilibrium Test (PET) and the Mass Transfer Area Coefficient (MTAC) were presented.

PET is a test of peritoneal membrane transport of solutes and water. Dialysis/Plasma (D/P) ratios of urea, creatinine and glucose were determined at weeks 0, 26 and 52. If peritonitis developed, a minimum of 30 days had to elapse between resolution of the peritonitis and the PET. The PET was used to calculate the MTAC that provides a measure of diffusive solute mass transport based on membrane permeability and surface area.

The PET D/P ratios were not significantly different for each timepoint between treatments.

For glucose at week 52 there was a suggestion of a difference in the MTAC results as follows:

Lab Assay	Visit	Treatment Group	Baseline [®]	Data			Change from Baseline [®]			pBetw
			Mean	N	Mean	SE	Mean	SE	pW/in	
MTAC for Creatinine	Baseline (Week 0)	Control		105	9.954	0.276				0.381
		Icodextrin		169	0.306	0.267				
	Week 26	Control	9.913	82	10.223	0.290	0.365	0.230	0.116	0.929
		Icodextrin	10.276	126	0.460	0.264	0.226	0.277	0.416	
	Week 52	Control	9.663	62	9.970	0.345	0.308	0.263	0.247	0.559
		Icodextrin	10.272	101	10.512	0.334	0.279	0.354	0.432	
MTAC for Urea	Baseline (Week 0)	Control		105	18.500	0.367				0.880
		Icodextrin		168	18.575	0.315				
	Week 26	Control	18.577	81	18.271	0.394	-0.163	0.420	0.698	0.784
		Icodextrin	18.690	126	18.523	0.380	-0.084	0.394	0.832	
	Week 52	Control	18.118	62	17.880	0.466	-0.238	0.461	0.607	0.436
		Icodextrin	18.561	101	18.550	0.473	0.026	0.543	0.961	
MTAC for Glucose	Baseline (Week 0)	Control		105	10.725	0.341				0.993
		Icodextrin		169	0.721	0.264				
	Week 26	Control	10.676	83	10.696	0.315	0.029	0.292	0.920	0.018
		Icodextrin	10.504	124	11.381	0.354	1.017	0.282	<0.001	
	Week 52	Control	10.339	62	10.899	0.436	0.560	0.398	0.164	0.197
		Icodextrin	10.192	99	11.378	0.385	1.263	0.343	<0.001	

[®] Baseline is the Week 0 Value. pW/in=p-Value from the within treatment group paired t-test for significant mean change from Baseline. pBetw=Baseline (Week 0): p-Value from analysis of variance testing for significant differences across treatment group means. Postbaseline (Treatment Weeks 26, 52): p-Value from analysis of covariance testing for significant differences across treatment groups for mean changes.

Comments

This safety study raises a serious question because of a unfavorable numerical mortality result suggesting that Icodextrin might increase the risk of death in ESRD patients compared to 2.5% Dextrose. While the difference in mortality was not statistically significant, neither does it support the conclusion that the two drugs are similar in terms of mortality risk.

The data were provided to support a clinical benefit related to Icodextrin administration, i.e. Quality of Life, edema status, and weight were not convincing due to incomplete data, inconsistency over time, and selection of timepoints, endpoints and conditions post-hoc.

3. ML/1B/001 (MIDAS): This was an open, randomized study performed at 11 centers in the UK with a product called Dextrin 20 that was essentially the same drug product as the Icodextrin formulation used in studies 130 and 131. Eligible patients were those adults on CAPD for at least three months, using 3-4 exchanges per 24 hours and free of peritonitis and mechanical drainage complications for at least 1 month prior to entry. The primary endpoint was the comparison of the median volume of ultrafiltrate at weeks 4, 13 and 21 (called special weeks by the protocol) produced after the long-dwell 12 hour dialysis with Dextrin 20 or the Dextrose solution (concentrations of 1.5%, 2.5% or 4.5%) as used prior to randomization for the ITT population (last value carried forward). Other secondary analyses involved different timepoints (weeks 3, 12 and 20 using an 8 hour long-dwell time), bag sizes (1.5 or 2.0L), subsets of the ITT population, and efficacy evaluable populations using the Bonferroni correction. Other analyses were done of “weak” glucose concentration i.e. 1.36%, “medium” i.e.2.3%, and “strong” i.e. 4.25% versus Dextrin 20.

209 patients were randomized, 103 to control and 106 to Dextrin 20. Some demographic features of the population were:

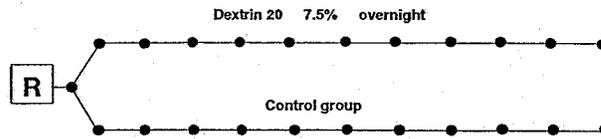
	Control n=103	Dextrin 20 n=106	Total n=209
Age, mean in years(SD)	55.2(15.0)	55.1(14.2)	55.2(14.6)
Male/Female	65%/35%	66%/34%	66%/34%
Caucasian	93%	90%	91%
Diabetes(%)	11(10.7%)	15(14%)	26(12.4%)

The type and duration of renal disease was provided as follows:

All Patients

	Control	Dextrin 20	Total
Number of Patients	103	106	209
Cause			
Glomerulonephritis	16 (16%)	17 (16%)	33 (16%)
Polycystic Kidney Disease	10 (10%)	10 (9%)	20 (10%)
Hypertension	24 (23%)	24 (23%)	48 (23%)
Pyelonephritis	10 (10%)	11 (10%)	21 (10%)
Congenital	2 (2%)	0 (0%)	2 (1%)
Diabetes Mellitus	8 (8%)	11 (10%)	19 (9%)
Other	33 (32%)	33 (31%)	66 (32%)
Duration (months)			
Mean (s.d.)	96.0 (88.9)	98.0 (113.3)	97.0 (101.8)
Median	67.9	64.8	65.7
Minimum	6.1	4.3	4.3
Maximum	460.2	639.0	639.0
n	102	105	207

The plan for the study was:



Week	1	2	3	4	5	7	9	13	17	21	25	
Visit	1	2	3†	4†	5†	6	7†	8†	9	10†	11†	12
12 hr overnight exchange for 7 nights (week)					X (4)				X (13)		X (21)	
BP, weight	X	X	X	X	X	X	X	X	X	X	X	X
MEs* and symptoms	X	X	X	X	X	X	X	X	X	X	X	X
Medication/changes	X	X	X	X	X	X	X	X	X	X	X	X
Diary check		X	X	X	X	X	X	X	X	X	X	X
Physical check	X											X
Medical history	X											
Haematology & biochemistry		X		X		X		X	X	X	X	X
Plasma Dextrin 20		X				X‡			X‡			X
Fasting lipids		X										X
Eye, ECG, X-ray		X										X
R.E. tests§		X										X
Creatinine clearance		X										X

R Randomisation

§ Optional

‡ Dextrin 20 group only

† These visits may take place at the patient's home

* ME = Medical Event

The monitoring schedule for RD-97-CA-131, the long term US safety study described above, included scheduled visits for the newly randomized patients at baseline, week 13 and every 13 weeks to week 52. Those entering from study RD-97-CA-130 had data at 2 and 4 weeks post baseline from that earlier study. As can be seen from the chart above, the UK study design had a more frequent visit schedule, and at each visit medical events and CAPD symptoms were assessed which formed part of the safety database.

The disposition of patients can be assessed from the chart below:

	Control	Dextrin 20
Number recruited	103	106
Number withdrawn permanently (up to/at Visit 2)	4 (4%)	10 (9%)
Loss of ultrafiltration	1	2
Problems with catheter	0	1
Apparently unrelated medical events	0	1
Patient wished to withdraw	1	2
Transplant	0	3
Other	2	1
Number in study at Visit 2	99	96
Number withdrawn temporarily	5 (5%)	11 (11%)
Number withdrawn permanently (after Visit 2)	28 (28%)	29 (30%)
Loss of ultrafiltration	1	3
Problems with catheter	1	1
Any adverse event	1	4
Patient out for ≥ 4 weeks	9	4
Patient wished to withdraw	3	4
Non-compliance	1	1
Transplant	5	6
Haemodialysis	2	2
Other	5	4
Number completing study	71 (72%)	67 (70%)

The case report forms included a temporary withdrawal form. Since patients were seen frequently where not only were diaries checked and symptoms elicited, where clinical circumstances indicated one temporary withdrawal period of up to a month to stabilize the patient on his/her usual pretrial CAPD regimen before reentering. To illustrate, patient 0608 was temporarily withdrawn on 6/21/91 for fluid overload, swollen ankles, shortness of breath and hypertension causing migraine, stabilized and reentered 7/15/91.

Results of the median ultrafiltrate volumes for the "total population and last values" at weeks 4, 13 and 21, where a 12 hour long-dwell time was used, were:

Special Week	n	Control Mean (s.d.)	n	Dextrin 20 Mean (s.d.)	Dextrin 20 - Control Difference in means (s.e.)	95% Confidence Interval
4	93	222.3 (420.9)	83	558.6 (284.8)	336.3 (54.8)	228.1 to 444.5
13	93	202.9 (408.6)	84	538.8 (283.4)	335.9 (53.4)	230.5 to 441.3
21	93	229.6 (416.8)	84	549.5 (288.8)	319.8 (54.5)	212.3 to 427.3

p=0.78 for test of non-constant treatment difference

p<0.0001 for test of overall treatment difference

At weeks 3, 12 and 20 where an 8 hour long-dwell time was used the overall results were similar.

This analysis subdivided by weak (1.36%) or medium or strong (2.27 or 3.84%) glucose concentrations suggested a larger benefit of Dextrin 20 versus those in the weak concentration group.

Special Week	n	Control Mean (s.d.)	n	Dextrin 20 Mean (s.d.)	Dextrin 20 - Control Difference in means (s.e.)	95% Confidence Interval
Weak (1.36%/1.5%)						
4	54	82.1 (342.5)	44	544.8 (296.4)	462.7 (65.5)	332.6 to 592.7
13	54	60.7 (334.0)	45	513.9 (289.0)	453.2 (63.5)	327.2 to 579.1
21	54	101.5 (349.9)	45	561.1 (293.3)	459.6 (65.7)	329.2 to 590.0
Medium (2.27%/2.3%) or strong (3.86%/4.25%)						
4	35	432.6 (453.6)	30	591.3 (246.5)	158.8 (92.8)	-26.6 to 344.1
13	35	405.4 (441.2)	30	593.3 (223.5)	187.9 (89.0)	10.0 to 365.8
21	35	413.6 (458.6)	30	552.5 (241.7)	138.9 (93.2)	-47.4 to 325.2
Weak : p = 0.93 for test of non-constant treatment difference p < 0.0001 for test of overall treatment difference						
Medium/Strong : p = 0.63 for test of non-constant treatment difference p = 0.06 for test of overall treatment difference						

The report does not provide the results for “medium” and “strong” glucose concentrations separately, and the literature report (Mistry et al: Kidney International, vol.46, 1994. Pp.496-503) gives the results as “weak: versus “strong” concentrations.

Regarding safety, there were 14 serious adverse events including 3 deaths; 2 in the Dextrose group and 1 in the Dextrin 20 group as detailed in the following chart:

	<u>CONTROL</u>		<u>DEXTRIN</u>	
M.I.	4	(0533) 0207* 0963* 0208	2	(0206) 0501
Cardiac failure	1	0317	1	0581**
Pneumonia	-		1	0724 ***
C.V.A.	-		2	0725# 0921
Severe hypertension	-		1	0902
Multiple emboli	1	0915	-	
Pulmonary embolism	-		1	(0913) @
	6		8	

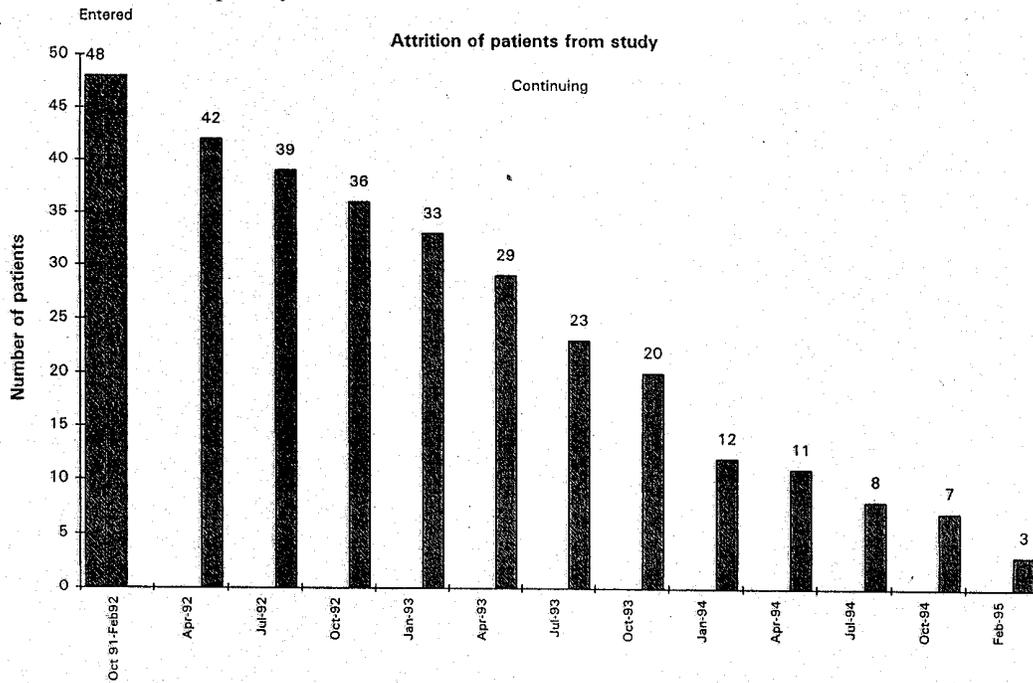
- * Death
- ** Asystole secondary to cardiac failure
- *** Before Dextrin commenced
- () Patients not withdrawn
- @ After nephrectomy (off Dextrin for 7 days previously)
- # Died 7 days later

Other findings of interest were 28 skin medical events (9 in control, 19 in Dextrin), and slight but statistically significant decline in serum sodium and chloride.

4. **ML/1B/004 MIDAS-2** was a long-term open, uncontrolled treatment extension of 48 Dextrin patients of the 67 Dextrin assigned completers from **MIDAS**. The report of MIDAS-2 covered 10/91 to 3/95 at which point 3 patients were continuing.

Of the 48 patients enrolled 36 were male and 12 were female. Their average age was 57 years and 8 were diabetics.

Attrition over time was portrayed as follows:



25 serious adverse events were reported including 12 deaths (three occurring after discontinuing Dextrin in patients 0266, 0961, 1202), and 5 withdrawals. The sponsor's listing of these cases was:

The following SAE has been reported since the report of 16 November 1994:

Patient No.	D.O.B.	Months of treatment	Date S.A.E.	S.A.E.	Outcome
0307	02.11.31	44	12.12.94	Continued ulcerated (R) toe	Withdrawn

For information, the previous SAE reports are given below together with information on total duration of icodextrin treatment:-

Patient No.	D.O.B.	Months of treatment	Date S.A.E.	S.A.E.	Patient Outcome
0104	09.12.40	14	00.06.92	Died at home	Deceased
0206	19.12.18	22	03.03.93	Bowel obstruction	Deceased
0211	01.07.30	23	00.05.93	Cardiac arrest	Deceased
0213	22.03.14	22	10.04.93	Bowel obstruction	Deceased
(0266	07.08.35	23	30.06.93	Cardiac arrest	Deceased♦)
0303	17.12.34	28	06.08.93	Skin cancer (R) forearm	Continued
0303	17.12.34	36	15.4.94	Necrotic leg ulcers	Continued
0303	17.12.34	40	13.7.94	Confusion/drowsiness (died 3.8.94)	Withdrawn
0307	02.11.31	21	02.12.92	(R) pleural effusions	Continued
0307	02.11.31	38	11.4.94	Proximal myopathy	Continued
0307	02.11.31	40	30.6.94	Infected R great toe	Continued
0309	16.02.26	18	24.09.92	Myocardial infarction	Continued
0316	29.01.21	33	25.01.94	Paralytic ileus	Continued
0316	29.01.21	34	14.02.94	Deep vein thrombosis	Deceased
0320	16.4.32	15	04.08.92	Bronchopneumonia	Deceased
0710	17.04.53	18	04.11.92	Respiratory arrest on haemodialysis	Withdrawn
0713	22.07.23	33	27.01.94	Cardiac arrest	Deceased
0907	30.07.26	28	04.08.93	Pleural effusions	Withdrawn*
0909	18.02.24	29	22.09.93	Died at home	Deceased
(0961	15.01.25	7	17.03.92	Died at home	Deceased@)
0964	27.11.21	25	09.07.93	Ischaemic (R) foot + gangrene	Continued
0964	27.11.21	26	09.08.93	Cardiac arrest after surgery	Deceased
(1202	02.05.28	10	05.05.92	Cardiac arrest after surgery	Deceased⊕)
1208	14.01.21	15	17.08.92	Severe dehydration	Withdrawn

♦ stopped icodextrin 00.05.93

* became named patient in compassionate use programme

@ stopped icodextrin 10.01.92

⊕ stopped icodextrin 00.02.92

Patient 719 who died of a GI bleed should be included in the above listing.

A substudy of net ultrafiltration in 12 patients gave results as follows: 1 month $424\text{ml} \pm 221\text{sd}$ (n=11); 3 months 418 ± 195 (n=12); 6 months 493 ± 197 (n=12); and 24 months 480 ± 280 (n=12).

While uncontrolled, given the low mortality rate on Dextrin in the 6 months of the Midas study, this follow-up of 72% of the Dextrin completers from the MIDAS study showed no early increase in deaths that might suggest a reason for the low mortality found in MIDAS.

5. PRO-RENAL: This was an open, randomized study of Icodextrin versus 2.27% glucose all utilizing one 2 liter bag for the long-dwell day exchange in 39 chronic stable APD adult peritoneal dialysis patients. Patients who had been hospitalized, were pregnant or lactating, had chronic exit site infections, HIV positive as well as other reasons were excluded. The duration of the study was 16 weeks including a 2 week baseline period, a 12 week treatment period and a 2 week follow-up period during which all patients used the control solution for the long-dwell exchange. The Icodextrin was provided as a single 2 L bag with the following composition:

COMPONENT	g/L	COMPONENT	mmol/L
Icodextrin	75	Sodium	133
Calcium Chloride Ph Eur	0.257	Calcium	1.75
Magnesium Chloride BP	0.051	Magnesium	0.25
Sodium Chloride Ph Eur	5.4	Chloride	96
Sodium lactate	4.5	Lactate	40
Water for injection Ph Eur	q.s. ad 1000 mL		

The composition of the control solution was:

COMPONENT	g/L	COMPONENT	mmol/L
Anhydrous Glucose BP	22.7	Sodium	132
Calcium Chloride Ph Eur	0.184	Calcium	1.25
Magnesium Chloride BP	0.051	Magnesium	0.25
Sodium Chloride Ph Eur	5.4	Chloride	95
Sodium lactate	4.5	Lactate	40
Water for injection Ph Eur	q.s. ad 1000 mL		

The study began on 1/21/97 and ended on 1/12/98. Eight European centers including Germany, France, the Netherlands and Belgium participated. The primary efficacy measure was net ultrafiltration for the long-dwell exchange (14±2hours) with peritoneal clearance of creatinine and urea as secondary variables. The ITT population was defined as all randomized patients and at least 1 long-dwell dialysis with the assigned solution. The evaluable population completed the 2 week baseline period and at least the first 6 weeks of the treatment period. Change from baseline was assessed at weeks 1, 6 and 12 with between treatment results analyzed.

Safety was assessed during the study period and any patient experiencing a serious adverse event was followed-up for 3 months. In addition to the usual laboratory tests, the protocol included assessments of carbohydrate absorption, changes in insulin requirements for diabetic subjects and was amended to include determination of the sodium content of the dialysate during the long-dwell exchanges. This was added to assess whether the decrease in serum sodium with Icodextrin noted in other studies was due at least in part to greater loss of sodium during the treatment dialyses.

The flowchart of procedures was:

	Baseline period		Treatment period					Follow-up period	
	-2	-1	+1	+2	+6	+12	+13	+14	
	VISIT	-I	+I	+2	+3	+4	+5		
INTERVALS	day -14	11 d ± 3 d	6 d ± 1 d 13 d ± 1 d	day 36-42	day 78-84	6 d ± 6 d ± 1 d ± 1 d			
Physical exam	#					#		#	
Vital signs	X	O	O	O	O	O	X	O	
Lab analyses (1)	X	O	O	O	O	O		O	
Concurrent Meds	X	O	O	O	O	O	X	O	
Review Compliance	X	O	O	O	O	O	X	O	
AE review	X	O	O	O	O	O	X	O	
RANDOMIZATION		X							
PET		X(2)				X(2)			
Lipids		O			O	O		O	
24 h urine coll.		O			O				
Icodextrin/Metab-Plasma		O	O	O	O	O	X	O	
Icodextrin - Dialysate		O	O	O	O	O		O	
14 h dialysate coll. (UF & analyses)		O	O	O	O	O		O	
Diabetic diary		O	O	O(3)					
HbA1c		O	X	O	O			O	

(1) : To include biochemistry, hematology with differential and platelets, plasma osmolality.
(2) : The PET must be performed the day after the dialysate & blood collections specified for the visit.
(3) : If needed.
O = To be performed at the patient's home
= To be performed by a physician

41 patients were screened, and 39 patients entered: 19 assigned to Dextrose and 20 to Icodextrin. Patient disposition was noted as follows:

Study Site	Screened	Treatment group	N° of patients entered	N° of patients completed	N° of patients withdrawn	
					AE	Other
ALL SITES	41	Control	19	16	3	
		Icodextrin	20	17	1	2
520: Hannover	5	Control	3	3		
		Icodextrin	2	1	1	
521: Dusseldorf	12	Control	6	5	1	
		Icodextrin	6	6		
522: Wurzburg	4	Control	2	2		
		Icodextrin	2	1		1
523: Colmar	4	Control	2	2		
		Icodextrin	2	2		
524: Pontoise	9	Control	3	2	1	
		Icodextrin	4	4		
525: Amsterdam	1	Control	0	0		
		Icodextrin	1	1		
526: Leuven	4	Control	2	1	1	
		Icodextrin	2	1		1
550: Cherbourg	2	Control	1	1		
		Icodextrin	1	1		

The baseline characteristics of those randomized were:

	Control Group		Icodextrin Group		All Patients		p-value
Age (yrs)							0.882 @
Number of patients	19		20		39		
Mean	45.4		46.1		45.7		
Std Error	3.45		3.01		2.25		
Minimum	26.0		27.0		26.0		
Maximum	75.0		74.0		75.0		
Gender	N	%	N	%	N	%	0.273 **
Male	13	68.4	17	85.0	30	76.9	
Female	6	31.6	3	15.0	9	23.1	
TOTAL	19	100.0	20	100.0	39	100.0	
Primary Renal Diagnosis	N	%	N	%	N	%	0.975 **
Diabetic nephropathy	2	10.5	2	10.0	4	10.3	
Hypertensive nephropathy	0	0.0	1	5.0	1	2.6	
Glomerulonephritis	7	36.8	9	45.0	16	41.0	
Polycystic kidney disease	2	10.5	1	5.0	3	7.7	
Interstitial nephritis	1	5.3	0	0.0	1	2.6	
Obstructive nephropathy	0	0.0	1	5.0	1	2.6	
Autoimmune disease	2	10.5	1	5.0	3	7.7	
Other	5	26.3	5	25.0	10	25.6	
TOTAL	19	100.0	20	100.0	39	100.0	
Race	N	%	N	%	N	%	1.000 **
Caucasian	19	100.0	19	95.0	38	97.4	
Asian	0	0.0	1	5.0	1	2.6	
TOTAL	19	100.0	20	100.0	39	100.0	

@ Analysis of Variance used to test for differences between treatment groups.

** Fisher Exact test used to test for differences between treatment groups because > 20% of the considered table's cells had expected counts < 5.

As noted under renal diagnosis, 4 diabetics entered. 2 were assigned to Dextrose and 2 to Icodextrin.

EFFICACY

The results for the primary efficacy variable of net UF were:

Treatment Group		(Baseline) Week -1	Week 1	Week 6	Week 12
Control	No. of patients	19	19	18	17
	Mean	-135	-137	-115	-166
	Standard error	88	79	94	101
	Minimum	-888	-852	-908	-713
	Maximum	617	383	664	727
	Mean change from baseline		-2	10	-20
	Min change from baseline		-386	-336	-331
	Max change from baseline		500	419	556
	p-Value for change from baseline		0.966	0.822	0.712
Icodextrin	No. of patients	20	20	18	17
	Mean	-175	323	292	206
	Standard error	55	64	48	38
	Minimum	-656	-112	-50	-126
	Maximum	266	967	615	418
	Mean change from baseline		498	472	378
	Min change from baseline		-251	-34	-105
	Max change from baseline		1131	1200	851
	p-Value for change from baseline		<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)	Icodextrin Adjusted Mean Change			442	p-Value ***
	Control Adjusted Mean Change			3	
	Difference (Icodextrin-Control) for Change			439	
	Std Error of Difference			67	
	Lower 90% Confidence Bound for Difference			328	
	Upper 90% Confidence Bound for Difference			551	

** The adjusted mean changes from the repeated measures analysis of covariance as calculated, with baseline value as the covariate, for each treatment group.

A 90% confidence interval was constructed around the difference between Icodextrin and Control.

*** p-value from the one-sided test for treatment differences using the repeated measures analysis of covariance.

The means of the long-dwell time and of the infused volumes was presented in the following two charts.

Table 11.4.4-1: Means of the Long Dwell Time (hour) at Each Visit

Visit	Group	N	Mean	Std Dev	Min	Max
Baseline (Week -1)	Control	19	13.5	1.3	11.8	15.8
	Icodextrin	20	13.5	0.9	12.1	15.3
Week 1	Control	19	13.5	1.3	10.2	15.8
	Icodextrin	20	13.8	1.3	12.0	16.7
Week 6	Control	18	13.2	1.3	11.3	15.2
	Icodextrin	18	13.4	1.3	12.1	15.2
Week 12	Control	17	13.1	1.2	12.0	16.0
	Icodextrin	17	13.3	0.8	12.1	15.0
Follow-up (Week 14)	Control	17	13.5	1.2	12.0	16.0
	Icodextrin	16	13.3	1.2	12.1	15.4

Table 11.4.4-2: Means of the infused volume for the long dwell (hour) at Each Visit

Visit	Group	N	Mean	Std Dev	Min	Max
Baseline (Week -1)	Control	19	1964	47	1879	2000
	Icodextrin	20	1933	73	1774	2000
Week 1	Control	19	1937	46	1861	2000
	Icodextrin	20	1902	38	1800	2000
Week 6	Control	18	1924	58	1772	2000
	Icodextrin	18	1876	74	1698	2000
Week 12	Control	17	1901	131	1423	2000
	Icodextrin	17	1891	73	1701	2000
Follow-up (Week 14)	Control	17	1914	100	1553	2000
	Icodextrin	16	1886	78	1700	2000

For the secondary variables of peritoneal creatinine and urea clearances respectively, results were:

Treatment Group		(Baseline) Week -1	Week 1	Week 6	Week 12
Control	No. of patients	19	19	18	17
	Mean	2.08	2.19	2.20	2.10
	Standard error	0.17	0.14	0.13	0.11
	Minimum	0.03	1.08	1.19	1.36
	Maximum	3.18	3.24	3.17	3.17
	Mean change from baseline		0.10	-0.00	-0.05
	Min change from baseline		-1.66	-0.51	-0.76
	Max change from baseline		1.67	0.43	0.72
	p-Value for change from baseline		0.511	0.999	0.553
Icodextrin	No. of patients	20	20	17	17
	Mean	2.10	2.55	2.66	2.54
	Standard error	0.07	0.10	0.11	0.09
	Minimum	1.52	1.76	1.68	1.64
	Maximum	2.85	3.24	3.29	3.00
	Mean change from baseline		0.45	0.58	0.46
	Min change from baseline		-0.04	0.04	-0.07
	Max change from baseline		1.23	1.58	0.99
	p-Value for change from baseline		<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)		Icodextrin Adjusted Mean Change			0.48
		Control Adjusted Mean Change			0.04
		Difference (Icodextrin-Control) for Change			0.43
		Std Error of Difference			0.10
		Lower 90% Confidence Bound for Difference			0.27
	Upper 90% Confidence Bound for Difference			0.60	
				p-Value ***	<0.001

** The adjusted mean changes from the repeated measures analysis of covariance, with baseline value as the covariate, for each treatment group.

A 90% confidence interval was constructed around the difference between Icodextrin and Control.

*** This p-value is from the one-sided test for treatment differences using the repeated measures analysis of covariance.

Treatment Group		(Baseline) Week -1	Week 1	Week 6	Week 12
Control	No. of patients	19	19	18	17
	Mean	2.21	2.28	2.34	2.27
	Standard error	0.19	0.14	0.15	0.14
	Minimum	0.05	1.29	1.16	1.38
	Maximum	3.50	3.25	3.56	3.58
	Mean change from baseline		0.07	0.01	-0.01
	Min change from baseline		-1.55	-0.50	-0.87
	Max change from baseline		1.66	0.49	0.80
	p-Value for change from baseline		0.637	0.846	0.957
Icodextrin	No. of patients	20	20	17	17
	Mean	2.17	2.62	2.74	2.63
	Standard error	0.08	0.10	0.12	0.09
	Minimum	1.48	1.80	1.80	1.65
	Maximum	2.94	3.28	3.34	3.11
	Mean change from baseline		0.45	0.59	0.47
	Min change from baseline		-0.23	-0.06	-0.17
	Max change from baseline		1.29	1.43	1.04
	p-Value for change from baseline		<0.001	<0.001	<0.001
OVERALL ** (From Repeated Measures)	Icodextrin Adjusted Mean Change			0.48	
	Control Adjusted Mean Change			0.06	
	Difference (Icodextrin-Control) for Change			0.42	p-Value ***
	Std Error of Difference			0.11	<0.001
	Lower 90% Confidence Bound for Difference			0.24	
	Upper 90% Confidence Bound for Difference			0.59	

** The adjusted mean changes from the repeated measures analysis of covariance, with baseline value as the covariate, for each treatment group.

A 90% confidence interval was constructed around the difference between Icodextrin and Control.

*** This p-value is from the one-sided test for treatment differences using the repeated measures analysis of covariance.

As with other studies, this study confirmed that for the long-dwell dialysis Icodextrin removes more fluid, creatinine and urea than 2.27% glucose. The sponsor noted that the result exceeded the 250 ml difference proposed in the protocol as the smallest meaningful clinical difference, however data were provided that a clinical benefit was associated with this physiological change.

SAFETY

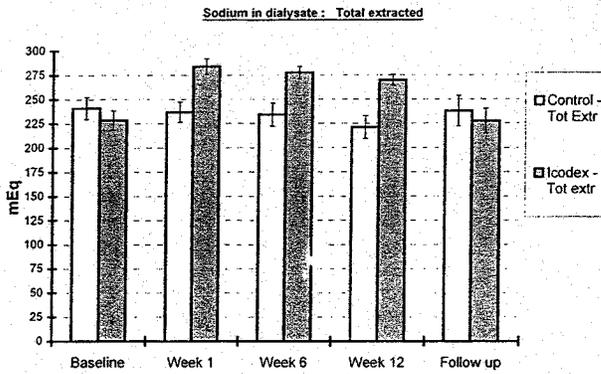
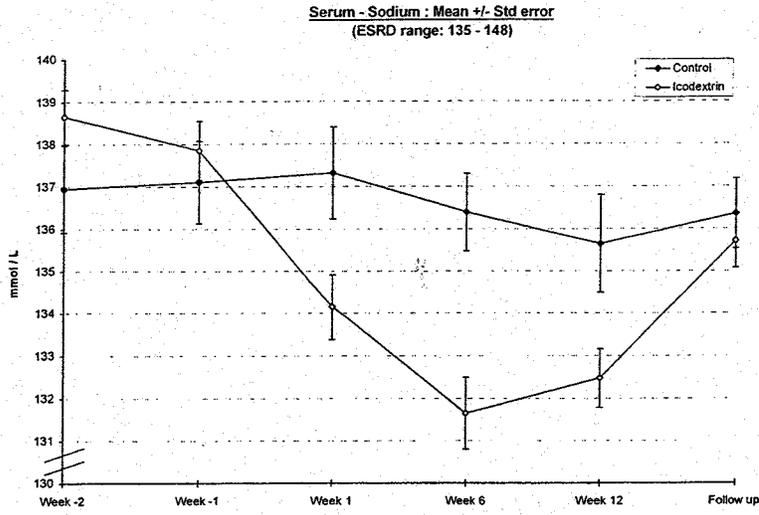
Of the 39 randomized patients, 6 withdrew for adverse reactions for the following reasons:

Treatment Group	Patient N°	Last study visit completed	Reason for withdrawal	Description
Control	0210	Week 13	Adverse event	Inguinal hernia
	0502	Week 1	Adverse event	Intraperitoneal leakage diagnosed as hernia
	0702	Week 6	Adverse event	Perforation of the stomach
Icodextrin	0103	Week 1	Adverse event	Peritonitis
	0304	Week 6	Death	Acute heart failure
	0703	Week 1	Transplantation	

While 1 death was noted during the trial, there were 2 other deaths in the Icodextrin group shortly after the treatment period. No deaths occurred in the Dextrose group. A brief narrative of those deaths follows. Patient 0304 was a 29 year old Caucasian male who had a history of hypertension for 2 years prior to entry on 4/8/97. On 5/27/97 BP was 150/80. Developed acute cardiac failure on 5/29/97 and died. Post mortem showed marked LVH and circulatory failure was listed as the cause of death. No acute MI was found. Patient 0801 was a 53 year old Caucasian female who entered the trial on 10/21/97, developed hypertension on 2/2/98, was switched to the control solution and became normotensive on 2/9/98. No date or cause of death given. Patient 0212 was a 59 year old Caucasian diabetic male who entered the trial on 11/6/97, was noted to have hypertension on 2/4/98 and had a stroke on 2/15/98. Presumably that was the cause of death on 2/21/98. 6 additional patients with serious adverse reactions were identified; 5 taking Dextrose and 1 on Icodextrin. The reactions were extraosseous calcification (history of hyperparathyroidism), inguinal hernia, hyperhydration, hernia, stomach perforation in the Dextrose group, and peritonitis in the Icodextrin group. These reactions were classified as serious because of the need for hospitalization. 56 other adverse reactions were noted; 25 in the control group and 31 in the Icodextrin group, most thought unrelated to drug treatment.

Laboratory abnormalities were found for serum sodium, chloride, alkaline phosphatase, serum amylase, and serum AST (SGOT) in direction and degree consistent with the findings of other studies.

The explorations of both serum and peritoneal sodium were more extensive with the following graphs depicting the patterns of change over time.



The change from baseline for carbohydrate absorption was somewhat greater in the Icodextrin arm compared to the Dextrose arm (+8gms/long-dwell versus +0.3gms/long-dwell, $p=0.003$). Of the 4 diabetic patients, 1 in the Dextrose arm required an increase in insulin. These safety data are not reassuring, since there was a numerically greater number of deaths in the Icodextrin group compared to control in this study where reasonably frequent clinical observations were made.

6. ML/1B/011 (DIANA): This was an open, randomized parallel study of Icodextrin 7.5% versus Dextrose (1.36% or 2.27% or 3.86%) for long-dwell dialysis in 38 adult ESRD adult APD patients. The electrolytic composition of the Control in mmol/liter was Sodium 132, Chloride 102, Calcium 1.75, Lactate 35, and Magnesium 0.75. For Icodextrin it was Sodium 133, Chloride 97, Calcium 1.75, Lactate 40, and Magnesium 0.25.

The duration of the study was two years, and it was conducted in the Netherlands at two hospitals (Rotterdam and Haarlem). The primary purposes of this study were to:

- A. Evaluate the safety, efficacy and biocompatibility of Icodextrin compared to Dextrose.
- B. To evaluate whether there was less damage to host resistance (macrophage function, peritonitis episodes) and to the peritoneal membrane with Icodextrin.
- C. To assess “whether the glycation of peritoneal membrane” was less with Icodextrin.

The following evaluations were to be made at approximately 3 month intervals:

SCHEDULE FOR CLINICAL AND LABORATORY MEASUREMENTS

Month	0	3	6	9	12	15	18	21	24
Visit	1	2	3	4	5	6	7	8	9
General									
Physical exam	0	0	0	0	0	0	0	0	0
weight	0	0	0	0	0	0	0	0	0
blood pressure	0	0	0	0	0	0	0	0	0
symptoms	0	0	0	0	0	0	0	0	0
medical events	0	0	0	0	0	0	0	0	0
Laboratory measurements									
Hb, ht, ery, plat, WBC	0	0	0	0	0	0	0	0	0
ASAT, ALAT	0	0	0	0	0	0	0	0	0
γGT, Alk.Phos	0	0	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0
Urea	0	0	0	0	0	0	0	0	0
Ca, P	0	0	0	0	0	0	0	0	0
Albumin	0	0	0	0	0	0	0	0	0
Glucose	0	0	0	0	0	0	0	0	0
*Osmolality	0	0	0	0	0	0	0	0	0
HbA _{1c}	0	0	0	0	0	0	0	0	0
Cholesterol	0	0	0	0	0	0	0	0	0
Triglycerides	0	0	0	0	0	0	0	0	0
HDL-chol	0	0	0	0	0	0	0	0	0
Dialysis related									
*MTAC	0	0	0	0	0	0	0	0	0
*UF	0	0	0	0	0	0	0	0	0
Residual vol.	0	0	0	0	0	0	0	0	0
KT/V	0	0	0	0	0	0	0	0	0
*Glucose load	0	0	0	0	0	0	0	0	0
Dextrin 20/metab	0	0	0	0	0	0	0	0	0
Peritonitis	0	0	0	0	0	0	0	0	0
Macrophage Fcγ receptor function	0				0				
Urinary measurements in 24-hour samples									
Volume	0	0	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0
Dextrin 20 / metab	0	0	0	0	0	0	0	0	0
In times of peritonitis									
MTAC									
UF									
Dextrin 20 / metab									
In vitro (effluent)									
* Peritoneal macrophage									
IL-1 production	0	0	0	0	0	0	0	0	0
Opsonin	0	0	0	0	0	0	0	0	0
IL-6, IL-8	0	0	0	0	0	0	0	0	0
TGF-β, TNF	0	0	0	0	0	0	0	0	0
*CA-125	0	0	0	0	0	0	0	0	0
*Procollagen	0	0	0	0	0	0	0	0	0
*Glycated albumin	0	0	0	0	0	0	0	0	0
Peritoneal histology									
Percutaneous biopsy	0	0	0	0	0	0	0	0	0
Surgical biopsy - when possible									
* Primary endpoints									

No formal estimation of sample size was done, and corrections for multiple endpoints were to be made appropriately.

The demographics of the 38 randomized patients were:

	TOTAL	GLUCOSE	ICODEXTRIN
Number of patients	38	19	19
Sex:			
male	27	17	10
female	11	2	9
Race:			
Asian	4	1	3
Caucasian	31	16	15
Afro-caribbean	2	1	1
other	1	1	0
Age (years)			
mean	52.18	51.42	52.95
sd	13.28	15.38	11.18
min	21	21	31
max	70	68	70
Diabetic	2	2	0

RENAL DISEASE AND APD HISTORY

	GLUCOSE	ICODEXTRIN
Main cause of renal disease		
glomerulonephritis	8	6
polycystic kidney disease	3	4
hypertension	1	5
pyelonephritis	1	0
congenital	1	0
diabetes	1	0
other	4	4
New to APD	5	5
Duration of APD (months) for established CCPD patients		
mean	29	21
sd	26	18
min	2	1
max	83	55
n	14	14
Current daytime regime		
dry	2	1
dry+CAPD	0	2
1.36	3	4
2.27	10	11
3.86	3	1
2.27+CAPD	1	0

The number of patients assessed at each timepoint was:

Month	0	3	6	9	12	15	18	21	24
N on Icodex.	19	19	18	15	12	11	9	7	7
N on Control	19	16	14	13	13	12	8	6	6

ITT and completer analyses were done, but insufficient data was collected for the biocompatibility endpoints specified in the protocol, such as IL-6 or TNF-", and where sufficient data were available, such as with macrophage function, no differences between groups were noted.

The only efficacy endpoint that did show a significant difference was net UF. At baseline both groups showed negative net ultrafiltration volumes. While this negative direction continued in those receiving Dextrose for the log-dwell dialysis, the UF volumes became positive for those assigned to Icodextrin.

Of greatest interest in this study are the safety results.

5 patients died during the study and 1 died two and one-half months after withdrawal from the study. All were in the Dextrose group. A brief cause of death for each patient follows.

A006/0006 66 year old Caucasian male-infection and sepsis after toe amputation.

A017/0017 66 year old Caucasian male-CVA.

A019/0019 68 year old Asian female-dehydration, hypotension, transferred to nursing home and died 4 months later.

A025/0025 57 year old diabetic Caucasian male-peritonitis due to bowel ischemia.

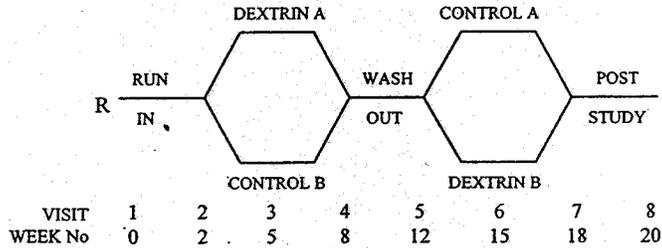
A027/0027 67 year old Caucasian male-myocardial infarction.

B010/0110 55 year old Caucasian male-acute necrotic pancreatitis.

While the Pro-Renal study results included 3 deaths all on Icodextrin, this study result shows an opposite numerical direction.

In addition to the deaths, 7 patients withdrew from the Dextrose group and 12 from the Icodextrin group. The major reason given was transplantation.

7. ML/1B 020 (DELIA): This was an open, single center randomized crossover study in 11 adult ESRD undergoing APD which compared Icodextrin to a dry dwell. The design of the study was as follows:



Of the 11 randomized patients, all were Caucasian, 3 were male and mean age was 51.9 years±13.6. 7 patients completed both study periods, and diabetes was the most frequent cause of the renal disease. For the completers, there was no significant difference in 24 hour total ultrafiltration volume for the Icodextrin arm versus the control arm. There was a significant increase in creatinine clearance during the Icodextrin treatment compared to control (47.4l/week±12.0 versus 29.5±8.7,p<0.01). Concerning safety, there were no deaths reported, there were 7 serious adverse reactions reported (4 in the Icodextrin period). 6 patients withdrew for peritonitis or diarrhea, 4 during the Icodextrin period.

8. RD-99-CA-060 and ML/1B/014 (MIDAS Substudy) were two pharmacokinetic studies; the first of a single Icodextrin exchange, and the second of Icodextrin levels at steady state, after stopping and after restarting Icodextrin. These will be reviewed in the Biopharmaceutics review, as will study **ML1B/002** that evaluated insulin absorption when administered intraperitoneally during CAPD with Icodextrin or glucose.

9. ML/1B 009 (IDEAL): This was an open, noncomparator study of Icodextrin in CAPD patients who had lost ultrafiltration across the peritoneum as defined by a PET study. Although the study planned to enroll 100 patients at 10 European centers and treat patients for 6 months, it was stopped after 16 patients enrolled in over a year. No efficacy data are presented, but safety data were reported. 8 males and 8 females entered at two centers; one in London, the other in Brussels. They ranged from 19 to 78 years of age. No other demographic data were presented. Patient disposition was detailed as follows:

Patient #, Disposition	Study Solution Receipt	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
101, Completed	Feb. 24, 1995	March 27, 1995	April 04, 1995	May 22, 1995	June 19, 1995	July 18, 1995	Sept. 04, 1995
102, Completed	March 17, 1995	April 18, 1995	May 15, 1995	June 12, 1995	July 10, 1995	Aug. 03, 1995	Sept. 04, 1995
301, Completed	Jan. 24, 1995	Feb. 24, 1995	March 24, 1995	April 26, 1995	May 26, 1995	June 30, 1995	July 28, 1995
302, Completed	Jan. 23, 1995	Feb. 24, 1995	March 31, 1995	April 27, 1995	May 19, 1995	June 30, 1995	July 19, 1995
303, WD 03/29/1995	Feb. 02, 1995	March 02, 1995					
304, Completed	Feb. 02, 1995	March 02, 1995	March 30, 1995	April 21, 1995	May 10, 1995	June 20, 1995	July 27, 1995
305, WD 05/30/1995	Feb. 21, 1995	March 21, 1995	April 24, 1995	May 24, 1995			
306, Completed	March 15, 1995	Apr. 04, 1995	May 03, 1995	June 06, 1995	July 28, 1995	Aug. 25, 1995	Sept. 26, 1995
307, WD 11/17/1995	July 26, 1995	Aug. 25, 1995	Sept. 29, 1995	Oct. 24, 1995			
308, WD 03/07/1996	Sept. 17, 1995	Oct. 04, 1995	Nov. 06, 1995	Dec. UNK, 1995	Jan. 09, 1996	Feb. 13, 1996	
309, WD Date UNK	NA	---					
1101, WD 07/13/1995	May 19, 1995	June 16, 1995	July 13, 1995				
1102, Completed	May 31, 1995	June 12, 1995	July 31, 1995	Sept. 01, 1995	Dec. 01, 1995	Jan. 08, 1996	Feb. 08, 1996
1103, Completed	May 30, 1995	June 23, 1995	July 31, 1995	Sept. 01, 1995	Oct. 03, 1995	Oct. 27, 1995	Dec. 01, 1995
1104, WD 08/18/1995	July 31, 1995	---					
1105, WD 01/16, 1996	Dec. 12, 1995	Jan. 05, 1996					

WD = Withdrawn

UNK = unknown

NA=Not applicable

--- Patient did not complete Visit 2

5 patients died. Those were:

patient 305-50 year old diabetic Caucasian female died after a myocardial infarction.

patient 307-77 year old Caucasian female had peritonitis and was not responding to dialysis.

patient 308-78 year old Caucasian male died after a myocardial infarction.

patient 1104-75 year old Caucasian male died in his sleep.

patient 1105-45 year old Caucasian male died after a cardiac arrest.

Each of these patients had a history of cardiovascular disease.

Other serious adverse reactions were reported by 5 patients. These included hypertension, CVA, overhydration, diabetic management problem, exit site infection, and peritonitis.

Without a randomized control group, it is difficult to assess the significance of these safety results.

VI. INTEGRATED REVIEW OF EFFICACY

The three controlled efficacy studies, 130, MIDAS, Pro-Renal, demonstrate That Icodextrin is an effective peritoneal dialysis drug, and is superior to 1.5% and 2.5% Dextrose for ultrafiltration amounts and creatinine and urea peritoneal clearance during the long-dwell period for CAPD and APD. Icodextrin long-dwell dialysis would be integrated into a daily treatment regimen which would still employ Dextrose for the other dialyses.

None of the patients entered were doing poorly on their regimen which consisted of Dextrose for all dialyses, but greater volumes of fluid and waste products were removed when Icodextrin was substituted for the long-dwell. The sponsor does not make a convincing case that this represents a clinical benefit were everyone to be treated with the new drug. In some cases excess fluid removal could lead to dehydration, hypotension, electrolyte imbalance. What attempts were made to show a clinical benefit, e.g QoL results, edema status, were not convincing because of incomplete cohort results, post-hoc selection of time points and scales, and inadequate statistical consideration of non-preplanned endpoints and multiple comparisons. That is not to say that the sponsor needs to prove that fluid and waste removal in ESRD is beneficial. Compared to historical expectations it is clear that Icodextrin is an effective dialysis drug, but compared to a currently used and well-tolerated drug there is no convincing data to demonstrate clinical superiority.

VII INTEGRATED REVIEW OF SAFETY

840 patients were included in the sponsor's integrated summary of safety; 493 assigned to Icodextrin and 347 to control. The breakdown by study was as follows:

Study	Control Group	Extraneal Group	Total Patients
Key Studies			
RD-97-CA-130	85	90	175
RD-97-CA-131	112	175	287
ML/IB/001 (MIDAS)	103	106	209
PRO-RENAL-REG-035	19	20	39
Total Key Studies	319	391	710
Supportive Studies			
ML/IB/011 (DIANA)	19	19	38
ML/IB/020 (DELIA)	9	10	19*
ML/IB/014 (MIDAS-2)	--	48	48
RD-99-CA-060	--	13	13
ML/IB/014 (S-5)	--	12	12
Total Supportive Studies	28	102	130
Total All Studies	347	493	840

*DELIA population data from Baxter. One patient received no drug and is not included in this table; 2 patients received icodextrin only; 1 received control only; a total of 12 patients were enrolled.

The duration of exposure was:

	Control Group N = 347	Extraneal Group N=493	All Patients N=840
Duration (days)			
Mean ± SE	174.3 ± 8.25	232.5 ± 11.06	208.5 ± 7.39
Minimum	2.0	2.0	2.0
Median	165.0	169.0	169.0
Maximum	807.0	1326.0	1326.0

Some demographic characteristics were:

	Control Group N = 347		Extraneal Group N = 493		All Patients N = 840	
Age (yrs)						
Mean ± SE	54.1 ± 0.76		53.9 ± 0.63		54.0 ± 0.48	
Range	19 – 86		18 – 83		18 – 86	
Weight (kgs)						
Mean ± SE	74.4 ± 0.82		75.6 ± 0.69		75.1 ± 0.53	
Range	44.4 – 145.4		37.0 – 140.5		37.0 – 145.4	
	Control Group		Extraneal Group		All Patients	
	n	%	n	%	n	%
Age Categories						
<35	33	9.5	52	10.5	85	10.1
35 - <45	63	18.2	70	14.2	133	15.8
45 - <55	65	18.7	113	22.9	178	21.2
55 - <65	91	26.2	135	27.4	226	26.9
65 - <75	76	21.9	102	20.7	178	21.2
>=75	19	5.5	21	4.3	40	4.8
Gender						
Male	175	50.4	278	56.4	453	53.9
Female	172	49.6	215	43.6	387	46.1
Race						
Caucasian	257	74.1	360	73.0	617	73.5
Hispanic	10	2.9	14	2.8	24	2.9
Asian	12	3.5	22	4.5	34	4.0
Black	62	17.9	90	18.3	152	18.1
Other	6	1.7	7	1.4	13	1.5

Reference: Appendix 8 Summary Table 3.0a.

Diabetic, hypertensive and hypertensive nephropathy subpopulations were represented as follows:

Table 3: Disease Subpopulations by Treatment Group		
	Control Group	Extraneal Group
Patients with Diabetes		
All Studies	94	132
Key Studies	92	116
Supportive Studies	2	16
Patients with Hypertension		
All Studies	147	243
Key Studies	134	188
Supportive Studies	13	55
Patients with Primary Diagnosis of Hypertensive Nephropathy		
All Studies	68	114
Key Studies	67	89
Supportive Studies	1	25

Reference: Appendix 8 Summary Tables 4.0a, 4.0.b, 4.0c

Disposition of patients was:

	Control Group		Extraneal Group	
	n	%	n	%
ALL STUDIES	N=347		N=493	
Completed Study	246	70.9	323	65.5
Prematurely Discontinued Study	101	29.1	170	34.5
Transplantation	16	4.6	32	6.5
Adverse experience	41	11.8	66	13.4
Death	9	2.6	17	3.4
Protocol violation	11	3.2	7	1.4
Other	24	6.9	48	9.7
KEY STUDIES	N=319		N=391	
Completed Study	232	72.7	271	69.3
Prematurely Discontinued Study	87	27.3	120	30.7
Transplantation	10	3.1	13	3.3
Adverse experience	38	11.9	51	13.0
Death	4	1.3	8	2.0
Protocol violation	11	3.4	7	1.8
Other	24	7.5	41	10.5
SUPPORTIVE STUDIES	N=28		N=102	
Completed Study	14	50.0	52	51.0
Prematurely Discontinued Study	14	50.0	50	49.0
Transplantation	6	21.4	19	18.6
Adverse experience	3	10.7	15	14.7
Death	5	17.9	9	8.8
Protocol violation	0	0	0	0
Other	0	0	7	6.9

Reference: Appendix 8 Summary Table 1.0

The mortality comparisons did not include all patients who died during and following the study. This will be presented later.

ADVERSE EVENTS

For adverse events occurring in 5% or more of patients by treatment group and all patients were presented as follows:

COSTART BODY SYSTEM Preferred Term	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
BODY GENERAL						
Peritonitis	88	25.4	130	26.4	218	26.0
Exit site infect	58	16.7	73	14.8	131	15.6
Pain	43	12.4	48	9.7	91	10.8
Headache	23	6.6	43	8.7	66	7.9
Pain abdo	20	5.8	39	7.9	59	7.0
Flu synd	21	6.1	35	7.1	56	6.7
Injury accid	14	4.0	31	6.3	45	5.4
Asthenia	27	7.8	28	5.7	55	6.5
Lab test abnorm	12	3.5	25	5.1	37	4.4
Pain chest	12	3.5	25	5.1	37	4.4
Pain back	18	5.2	22	4.5	40	4.8
Infect	19	5.5	21	4.3	40	4.8
CARDIOVASCULAR						
Hypertens	29	8.4	62	12.6	91	10.8
Hypotens	37	10.7	32	6.5	69	8.2
DIGESTIVE						
Diarrhea	33	9.5	40	8.1	73	8.7
Nausea	17	4.9	35	7.1	52	6.2
Nausea vomit	21	6.1	25	5.1	46	5.5
Dyspepsia	13	3.7	25	5.1	38	4.5
Vomit	19	5.5	22	4.5	41	4.9
HEMATOLOGIC & LYMPHATIC						
Anemia	39	11.2	55	11.2	94	11.2
METABOLIC & NUTRITION						
Hypokalem	37	10.7	34	6.9	71	8.5
Hypoproteinem	32	9.2	34	6.9	66	7.9
Hypervolem	20	5.8	28	5.7	48	5.7
Edema	17	4.9	28	5.7	45	5.4
Hyperphosphatem	26	7.5	25	5.1	51	6.1
Hyperglycem	12	3.5	25	5.1	37	4.4
Edema periph	29	8.4	18	3.7	47	5.6
MUSCULOSKELETAL						
Arthralgia	27	7.8	31	6.3	58	6.9

COSTART BODY SYSTEM Preferred Term	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
NERVOUS						
Dizziness	19	5.5	27	5.5	46	5.5
RESPIRATORY						
Upper res infect	46	13.3	74	15.0	120	14.3
Cough inc	13	3.7	35	7.1	48	5.7
Dyspnea	24	6.9	26	5.3	50	6.0
SKIN						
Rash	16	4.6	50	10.1	66	7.9
Pruritus	23	6.6	27	5.5	50	6.0
Skin dis	18	5.2	11	2.2	29	3.5

Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Some events of interest were peritonitis, hyperglycemia, edema and rash. Episodes of peritonitis were similar between groups as was hyperglycemia. Edema was more frequently noted in the control group, and has been discussed in the results of individual studies. Rash was approximately twice as frequent in the Icodextrin treated patients and deserves further comment.

A breakdown by study of skin adverse events leading to discontinuation was:

Study	Patient ID	Preferred Term	Study Day at Onset of AE	Relationship to Study Drug	Severity Assessment
RD-97-CA-131	37301	Derm exfol	19	Definite	Mild
RD-97-CA-131	2401	Pruritus	52	None	Mild
RD-97-CA-131	17201	Pruritus	51	Possible	Severe
RD-97-CA-130	22101	Rash	1	Probable	Mild
RD-97-CA-130	33106	Rash	6	Probable	Moderate
RD-97-CA-131	19503	Rash	7	Possible	Severe
RD-97-CA-131	24401	Rash	5	Probable	Severe
RD-97-CA-131	37301	Rash	5	Definite	Moderate
RD-97-CA-131	45401	Rash	9	Probable	Moderate
RD-97-CA-131	33305	Rash vesic bull	21	Possible	Moderate
RD-97-CA-130	23208	Skin discolor	8	Probable	Mild
MIDAS-2	303	Ulcer skin	1210	None	Severe
MIDAS-2	307	Ulcer skin	1334	None	Moderate
RD-97-CA-130	23210	Urticaria	9	Probable	Severe

Reference: Appendix 8 Summary Table 17.0

All were treated with Icodextrin although patient 307 had been assigned to Control in MIDAS-1 and Icodextrin in MIDAS-2.

For skin events judged related to study drug, 14 patients on control (4.0%) reported such events versus 49 patients on Icodextrin (9.9% ; p<0.001).

By gender the following skin events were noted:

COSTART Preferred Term	Males				Females			
	Control Group (N=175)		Extraneal Group (N=278)		Control Group (N=172)		Extraneal Group (N=215)	
	n	%	n	%	n	%	n	%
Derm exfol	0	0	1	0.4	1	0.6	8	3.7
Eczema	0	0	2	0.7	1	0.6	4	1.9
Furunculosis	4	2.3	5	1.8	0	0	0	0
Herpes zoster	5	2.9	1	0.4	4	2.3	1	0.5
Nail dis	0	0	1	0.4	2	1.2	4	1.9
Pruritus	10	5.7	11	4.0	14*	8.1*	16	7.4
Rash	4	2.3	19	6.8	12	7.0	31	14.4
Rash vesic bull	5	2.9	5	1.8	4	2.3	1	0.5
Skin dis	6	3.4	5	1.8	12	7.0	6	2.8
Skin dry	1	0.6	8	2.9	2	1.2	2	0.9
Ulcer skin	3	1.7	9	3.2	10	5.8	7	3.3

*Values for "pruritus" include one control patient with preferred term "pruritis"

Exfoliative dermatitis and rash appear to be more frequent complaints in females.

Adverse events leading to discontinuation of the drug assigned were:

COSTART Body System Preferred Term	Control Group (N=347)		Extraneal Group (N=493)		All Patients (N=840)	
	n	%	n	%	n	%
BODY GENERAL						
Peritonitis	14	4.0	18	3.7	32	3.8
Pain	3	0.9	1	0.2	4	0.5
Pain back	2	0.6	1	0.2	3	0.4
Asthenia	3	0.9	0	0	3	0.4
Pain abdo	3	0.9	0	0	3	0.4
Hernia	2	0.6	0	0	2	0.2
CARDIOVASCULAR						
Heart arrest	3	0.9	7	1.4	10	1.2
Infarct myocard	4	1.2	4	0.8	8	1.0
Hypotension	4	1.2	1	0.2	5	0.6
DIGESTIVE						
Obstruct intest	1	0.3	3	0.6	4	0.5
Hem GI	1	0.3	3	0.6	4	0.5
Nausea vomit	4	1.2	2	0.4	6	0.7
Anorexia	2	0.6	0	0	2	0.2
Nausea	2	0.6	0	0	2	0.2
HEMATOLOGIC & LYMPHATIC						
Anemia	3	0.9	2	0.4	5	0.6
METABOLIC & NUTRITION						
Dehydrat	4	1.2	3	0.6	7	0.8
Electrolyte abnorm	2	0.6	2	0.4	4	0.5
Hypervolem	2	0.6	1	0.2	3	0.4
Hypovolem	2	0.6	1	0.2	3	0.4
Hypokalem	4	1.2	0	0	4	0.5
Ultrafil dec	2	0.6	0	0	2	0.2
NERVOUS						
Insomnia	2	0.6	2	0.4	4	0.5
SKIN						
Rash	0	0	6	1.2	6	0.7

Only one event per patient per preferred term was counted.

Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Proportions were similar between groups, though rash was a more frequent reason in Icodextrin treated patients.

SUBGROUPS: GENDER, AGE, RACE, DIABETES

By gender and treatment group the comparative incidence of selected adverse events was:

COSTART Body System Preferred Term	Control Group				Extraneal Group			
	Male N=175		Female N=172		Male N=278		Female N=215	
	n	%	n	%	n	%	n	%
CARDIOVASCULAR								
Angina pectoris	2	1.1	3	1.7	11	4.0	1	0.5
Cardiac murmur	1	0.6	0	0	2	0.7	8	3.7
Heart arrest	1	0.6	2	1.2	10	3.6	1	0.5
Hypertension	16	9.1	13	7.6	28	10.1	34	15.8
Hypotension	13	7.4	24	14.0	23	8.3	9	4.2
DIGESTIVE								
Dyspepsia	9	5.1	4	2.3	13	4.7	12	5.6
Nausea	7	4.0	10	5.8	12	4.3	23	10.7
Vomit	10	5.7	9	5.2	8	2.9	14	6.5
HEMATOLOGIC AND LYMPHATIC								
Anemia	12	6.9	27	15.7	28	10.1	27	12.6
Leukocytosis	1	0.6	3	1.7	5	1.8	10	4.7
METABOLIC AND NUTRITION								
Edema	6	3.4	11	6.4	14	5.0	14	6.5
Edema periph	11	6.3	18	10.5	5	1.8	13	6.0
Hypercalcem	2	1.1	8	4.7	10	3.6	7	3.3
Hyperglycem	4	2.3	8	4.7	15	5.4	10	4.7
Hyperphosphatem	8	4.6	18	10.5	10	3.6	15	7.0
Hypervolem	7	4.0	13	7.6	11	4.0	17	7.9
Hypoglycem	0	0	9	5.2	4	1.4	2	0.9
Hypokalem	12	6.9	25	14.5	12	4.3	22	10.2
Hypoproteinem	6	3.4	26	15.1	17	6.1	17	7.9
MUSCULOSKELETAL								
Arthralgia	11	6.3	16	9.3	10	3.6	21	9.8
NERVOUS								
Neuritis periph	1	0.6	10	5.8	1	0.4	7	3.3
RESPIRATORY								
Cough inc	5	2.9	8	4.7	15	5.4	20	9.3
Dyspnea	6	3.4	18	10.5	11	4.0	15	7.0
Upper res infect	23	13.1	23	13.4	39	14.0	35	16.3
SKIN								
Derm exfol	0	0	1	0.6	1	0.4	8	3.7
Pruritus*	10	5.7	14	8.1	11	4.0	16	7.4
Rash	4	2.3	12	7.0	19	6.8	31	14.4
Skin dis	6	3.4	12	7.0	5	1.8	6	2.8
Ulcer skin	3	1.7	10	5.8	9	3.2	7	3.3
SPECIAL SENSES								
Ear dis	1	0.6	2	1.2	1	0.4	9	4.2
UROGENITAL								
Infect urin tract	4	2.3	12	7.0	9	3.2	4	1.9

* Includes one female control patient with preferred term "pruritis."

Hypertension seemed more frequent in the Icodextrin treated females versus control females, but the hypotension result was in the opposite direction. Nausea was also somewhat more frequent in Icodextrin treated females compared to control treated females, but was similar to males treated with Icodextrin. Rash was most frequently reported in Icodextrin treated females.

In the geriatric population versus all patients, the results were:

COSTART BODY SYSTEM Preferred Term	Control Group				Extraneal Group			
	≥ 65 years N=95		All Studies N=347		≥ 65 years N=123		All Studies N=493	
	n	%	n	%	n	%	n	%
CARDIOVASCULAR								
Hypertension	7	7.4	29	8.4	7	5.7	62	12.6
Hypotension	12	12.6	37	10.7	11	8.9	32	6.5
Vasc dis periph	8	8.4	13	3.7	7	5.7	17	3.4
HEMATOLOGIC & LYMPHATIC								
Anemia	11	11.6	39	11.2	7	5.7	55	11.2
Leukocytosis	0	0	4	1.2	7	5.7	15	3.0
METABOLIC & NUTRITION								
Dehydration	8	8.4	17	4.9	11	8.9	23	4.7
NERVOUS								
Dizziness	8	8.4	19	5.5	10	8.1	27	5.5
SKIN								
Pruritus	11	11.6	23	6.6	4	3.3	27	5.5
Rash	6	6.3	16	4.6	10	8.1	50	10.1

Reference: Appendix 8 Summary Tables 9.0a, 14.1a

Most results between groups were of comparable frequency.

Concerning race comparative results for Caucasian and Black were provided:

COSTART BODY SYSTEM Preferred Term	Control Group				Extraneal Group			
	Caucasian N= 257		Black N=62		Caucasian N=360		Black N=90	
	n	%	n	%	n	%	n	%
BODY GENERAL								
Exit site infect	40	15.6	10	16.1	64	17.8	5	5.6
Flu syndrome	18	7.0	2	3.2	29	8.1	2	2.2
Headache	18	7.0	3	4.8	21	5.8	17	18.9
Pain chest	10	3.9	1	1.6	16	4.4	7	7.8
CARDIOVASCULAR								
Hypertens	19	7.4	7	11.3	32	8.9	23	25.6
Hypotens	18	7.0	14	22.6	21	5.8	9	10.0
Syncope	3	1.2	4	6.5	2	0.6	1	1.1
DIGESTIVE								
Diarrhea	21	8.2	10	16.1	31	8.6	6	6.7
Gastritis	1	0.4	6	9.7	5	1.4	3	3.3
Nausea	12	4.7	1	1.6	26	7.2	6	6.7
Nausea vomit	14	5.4	5	8.1	23	6.4	2	2.2
Vomit	19	7.4	0	0	17	4.7	3	3.3
HEMATOLOGIC AND LYMPHATIC								
Anemia	25	9.7	10	16.1	40	11.1	11	12.2
METABOLIC AND NUTRITION								
Edema	9	3.5	7	11.3	20	5.6	8	8.9
Edema periph	18	7.0	7	11.3	9	2.5	5	5.6
Hyperglycem	6	2.3	6	9.7	23	6.4	2	2.2
Hyperphosphatem	22	8.6	2	3.2	21	5.8	1	1.1
Hypoglycem	3	1.2	6	9.7	5	1.4	1	1.1
Hypokalem	23	8.9	13	21.0	18	5.0	13	14.4
Hypoproteinem	19	7.4	11	17.7	26	7.2	8	8.9
Hypovolem	2	0.8	4	6.5	6	1.7	2	2.2
Phosphatase alk inc	2	0.8	4	6.5	11	3.1	3	3.3
MUSCULOSKELETAL								
Arthralgia	23	8.9	2	3.2	21	5.8	6	6.7
RESPIRATORY								
Rhinitis	8	3.1	4	6.5	10	2.8	7	7.8
Upper res infect	36	14.0	7	11.3	59	16.4	10	11.1
SKIN								
Herpes zoster	3	1.2	4	6.5	2	0.6	0	0
Pruritus*	17	6.6	1	1.6	17	4.7	4	4.4
Rash	11	4.3	3	4.8	36	10.0	8	8.9

* Includes one female Caucasian control patient with preferred term "pruritus."

Reference: Appendix 8 Summary Tables 16.0a and 16.3a

Exit site infections seemed least frequent in Blacks on Icodextrin, while headache was most frequent in this group. Rather than put credence in these findings, one should be very cautious in any of the many numerical differences found in these exhaustive comparisons.

For diabetics versus all patients the results for selected adverse events were:

COSTART BODY SYSTEM Preferred Term	All Studies Population				Diabetic Subpopulation			
	Control Group (N=347)		Extraneal Group (N=493)		Control Group (N=94)		Extraneal Group (N=132)	
	n	%	n	%	n	%	n	%
BODY GENERAL								
Asthenia	27	7.8	28	5.7	12	12.8	13	9.8
Injury accid	14	4.0	31	6.3	6	6.4	16	12.1
Lab test abnorm	12	3.5	25	5.1	6	6.4	19	14.4
Pain back	18	5.2	22	4.5	8	8.5	3	2.3
CARDIOVASCULAR								
Hypotens	37	10.7	32	6.5	15	16.0	14	10.6
DIGESTIVE								
Diarrhea	33	9.5	40	8.1	15	16.0	11	8.3
Nausea	17	4.9	35	7.1	4	4.3	14	10.6
HEMATOLOGIC & LYMPHATIC								
Anemia	39	11.2	55	11.2	14	14.9	25	18.9
Leukocytosis	4	1.2	15	3.0	3	3.2	12	9.1
METABOLIC & NUTRITION								
Hyperglycem	12	3.5	25	5.1	11	11.7	21	15.9
Hypochlorem	3	0.9	8	1.6	0	0.0	7	5.3
Hypoglycem	9	2.6	6	1.2	8	8.5	6	4.5
Hypokalem	37	10.7	34	6.9	18	19.1	12	9.1
Hyponatrem	7	2.0	11	2.2	2	2.1	10	7.6
Hypoproteinem	32	9.2	34	6.9	14	14.9	21	15.9
SKIN								
Rash	16	4.6	50	10.1	5	5.3	14	10.6
Skin dis	18	5.2	11	2.2	10	10.6	7	5.3

Reference: Appendix 8 Summary Tables 9.0a and 33.0a

Since Icodextrin was developed with one expectation that it would provide less glucose load to diabetics and therefore be better tolerated, it is interesting that hyperglycemia was slightly more frequently reported in diabetics taking Icodextrin. Rash was also more frequent in this group.

Metabolic events were also compared in diabetics versus all patients:

COSTART Preferred Term	All Studies Population				Diabetic Subpopulation			
	Control Group (N=347)		Extraneal Group (N=493)		Control Group (N=94)		Extraneal Group (N=132)	
	n	%	n	%	n	%	n	%
Edema	17	4.9	28	5.7	9	9.6	12	9.1
Hypercalcem	10	2.9	17	3.4	2	2.1	8	6.1
Hypercholesterem	8	2.3	10	2.0	6	6.4	3	2.3
Hyperglycem	12	3.5	25	5.1	11	11.7	21	15.9
Hyperphosphatem	26	7.5	25	5.1	11	11.7	12	9.1
Hypochlorem	3	0.9	8	1.6	0	0.0	7	5.3
Hypocholesterem	1	0.3	6	1.2	0	0.0	6	4.5
Hypoglycem	9	2.6	6	1.2	8	8.5	6	4.5
Hypokalem	37	10.7	34	6.9	18	19.1	12	9.1
Hypomagnesem	4	1.2	7	1.4	4	4.3	2	1.5
Hyponatrem	7	2.0	11	2.2	2	2.1	10	7.6
Hypoproteinem	32	9.2	34	6.9	14	14.9	21	15.9
Phosphatase alk inc	6	1.7	14	2.8	5	5.3	6	4.5
Ultrafil dec	6	1.7	2	0.4	3	3.2	0	0.0

Reference: Appendix 8 Summary Tables 9.0a and 33.0a

For many comparisons diabetics had events more frequently than all patients (and nondiabetics by subtraction). Hypercalcemia and hyperglycemia was somewhat more frequent in diabetics treated with Icodextrin. Hypokalemia was more frequently reported in diabetics on the control drug.

LABORATORY FINDINGS

The sponsor provided summary information on the following laboratory parameters: serum sodium, serum chloride, alkaline phosphatase, serum amylase, and osmolality which results are presented below.

Serum Sodium

Table 27: Mean Values and Mean Changes From Baseline in Sodium (mmol/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	341	138.431	0.195	--	--
	Extraneal	472	138.530	0.160	--	--
One Month	Control	269	138.141	0.241	-0.242	0.209
	Extraneal	299	135.592	0.212	-2.744	0.217
3 Months	Control	217	138.180	0.234	-0.343	0.230
	Extraneal	265	135.694	0.211	-2.924	0.233
6 Months	Control	173	138.075	0.288	-0.578	0.320
	Extraneal	262	135.340	0.208	-3.597	0.224
1+ Year	Control	80	138.338	0.440	0.038	0.490
	Extraneal	157	135.752	0.245	-3.142	0.310
Last Visit	Control	329	138.161	0.214	-0.272	0.219
	Extraneal	451	135.796	0.156	-2.771	0.180

SE=standard error

Serum Chloride

Table 28: Mean Values and Mean Changes From Baseline in Chloride (mmol/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	268	96.795	0.301	--	--
	Extraneal	374	96.902	0.275	--	--
One Month	Control	216	97.319	0.344	0.633	0.244
	Extraneal	253	94.747	0.296	-1.729	0.282
3 Months	Control	177	98.264	0.402	0.485	0.306
	Extraneal	227	95.203	0.298	-2.325	0.301
6 Months	Control	142	98.761	0.448	0.567	0.399
	Extraneal	210	95.862	0.333	-2.538	0.349
1+ Year	Control	79	97.165	0.514	0.764	0.584
	Extraneal	136	94.566	0.631	-2.435	0.803
Last Visit	Control	285	97.627	0.306	0.610	0.263
	Extraneal	395	95.149	0.291	-2.003	0.348

SE=standard error

Alkaline Phosphatase

Table 31: Mean Values and Mean Changes From Baseline in Alkaline Phosphatase (U/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	214	89.107	3.667	--	--
	Extraneal	294	92.476	3.315	--	--
One Month	Control	167	85.383	3.547	-2.527	1.292
	Extraneal	192	110.068	5.164	15.142	2.194
3 Months	Control	116	92.724	5.169	1.096	5.034
	Extraneal	165	98.533	3.778	13.417	1.953
6 Months	Control	85	100.600	6.244	6.607	6.171
	Extraneal	132	100.924	3.902	15.800	3.700
1+ Year	Control	66	102.818	7.043	6.769	7.068
	Extraneal	104	111.423	10.401	24.864	10.525
Last Visit	Control	208	93.625	3.745	4.039	2.885
	Extraneal	278	111.428	5.251	19.073	4.247

SE=standard error

Serum Amylase

Table 30: Mean Values and Mean Changes From Baseline in Serum Amylase (U/L) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Baseline	Control	216	96.444	3.577	--	--
	Extraneal	286	98.623	3.499	--	--
One Month	Control	169	107.527	8.508	-1.677	1.780
	Extraneal	136	19.435	1.314	-95.198	5.201
3 Months	Control	119	112.235	14.233	-4.414	2.590
	Extraneal	131	29.053	2.590	-81.115	5.630
6 Months	Control	89	118.921	16.947	-5.824	3.625
	Extraneal	92	21.837	2.576	-95.304	6.798
1+ Year	Control	66	92.985	6.063	-6.045	4.042
	Extraneal	61	17.311	1.304	-108.426	7.639
Last Visit	Control	212	105.524	7.659	-3.784	2.179
	Extraneal	221	27.517	1.972	-81.004	4.343

SE=standard error

Plasma Osmolality

Table 29: Mean Values and Mean Changes From Baseline in Osmolality (mOsm/kg) – All Studies

Visit	Treatment Group	N	Data		Change From Baseline	
			Mean	SE	Mean	SE
Osmolality						
Baseline	Control	325	313.571	0.800	--	--
	Extraneal	441	312.986	0.663	--	--
One Month	Control	264	312.061	0.843	-1.152	0.896
	Extraneal	286	316.465	1.011	4.011	1.020
3 Months	Control	212	313.571	1.183	0.172	1.223
	Extraneal	251	314.100	0.850	0.927	1.102
6 Months	Control	165	310.234	1.012	-2.525	1.170
	Extraneal	238	313.987	0.821	0.384	1.005
1+ Year	Control	78	312.206	1.692	-1.526	1.853
	Extraneal	150	315.167	1.110	0.901	1.456
Last Visit	Control	325	312.111	0.806	-1.451	0.873
	Extraneal	427	314.365	0.707	1.404	0.831
Osmolality-Vapor Pressure						
Baseline	Control	16	317.813	3.389	--	--
	Extraneal	18	310.500	1.833	--	--
One Month	Control	15	315.000	2.920	-2.333	1.489
	Extraneal	18	314.111	1.501	3.611	2.108
3 Months	Control	16	313.875	3.487	-3.938	2.957
	Extraneal	16	315.125	1.281	4.250	2.120
Last Visit	Control	16	313.875	3.487	-3.938	2.957
	Extraneal	18	314.944	1.159	4.444	1.910

SE=standard error

In studies 130 and 131 decreases in serum sodium and chloride as well as serum cholesterol, amylase and AST (SGOT), and increases in alkaline phosphatase and plasma osmolality were statistically significant. The decreases in serum sodium and chloride are more likely due to increased loss in the dialysate during Icodextrin treatment per the results in the Pro-Renal study.

MORTALITY

The mortality result of study 131 has been discussed in that section above.

The initial results were provided for those who died during the study or within 30 days after completion or withdrawal. These initial results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1027.3	5	0.005	0.000	0.120	0.06	0.00	1.44
Icodextrin	175	1600.3	13	0.008	0.000	0.156	0.10	0.00	1.88

With follow-up for 13 months post-enrollment of all randomized patients, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1356.1	9	0.007	0.000	0.141	0.08	0.00	1.69
Icodextrin	175	2009.6	20	0.010	0.000	0.174	0.12	0.00	2.09

For all deaths reported in study 131, the results were:

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1364.2	12	0.009	0.000	0.163	0.11	0.00	1.96
Icodextrin	175	2022.9	22	0.011	0.000	0.182	0.13	0.00	2.19

In this summary section all deaths reported in the controlled studies submitted in the NDA were evaluated.

Overview tables follow:

Controlled Studies

Study	N in Study	Duration of Study	Icodextrin		Dextrose	
			Deaths	%	Deaths	%
131	287	52 weeks	22	12.6	12	10.7
MIDAS	206	6 months	1	0.9	2	1.9
PRO-RENAL	39	16 weeks	3	15	0	0
DIANA	32	2 years	0	0	6	31.6

Uncontrolled Studies

Study	N in Study	Duration of Study	Icodextrin	
			N	%
Ideal	16	6 months	5	31
Midas II	48	53 months	12	25

For all controlled studies, the sponsor provided an analysis of all deaths as follows:

**Mortality Analysis Including Additional Follow-up Data
Based on Survival Times in Days – Survivors Have Censored Times**

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	285	20	7.0	481	558	N/A	508.0 #	12.62	487.3	528.8	0.929
Icodextrin	366	26	7.1	704	N/A	N/A	636.3 #	17.68	607.2	665.4	
TOTALS	651	46	7.1	541	N/A	N/A	602.6 #	17.66	573.5	631.6	

* p-Value is from the LogRank test comparing the survival curves between groups.
The mean and standard error were underestimated because the largest observation was censored.
N/A: there were not enough deaths to estimate this quartile.

Mortality Rates (per Month and per Year) Based on Poisson Estimation

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	285	2268.7	20	0.009	0.000	0.163	0.11	0.00	1.96
Icodextrin	366	2926.7	26	0.009	0.000	0.164	0.11	0.00	1.97

@ the estimated mean and 90% confidence interval are displayed.

Differences Between Mortality Rates (per Month and per Year) Based on Poisson Estimation

Equivalence of Icodextrin and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin Mean	Control Mean	Difference (Ico - Cntl)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Cntl)	Lower 90%	Upper 90%
0.009	0.009	0.000	0.0026	-0.004	0.004	0.001	-0.051	0.053

These pooled results do not support an increased mortality risk in patients treated with Icodextrin compared to control. None of the individual study or pooled mortality comparisons were statistically significant. However, no study was sized to demonstrate a significant difference, and the adverse numerical result in study 131 was something of a surprise. While the most likely explanation for that result is chance, what was set out to be demonstrated, i.e. that Icodextrin and control had similar mortality risks, was not demonstrated. Rather than dismiss the study 131 finding, an additional long-term mortality study should be considered with the objective to rule out some predetermined mortality risk increase, taking into account the size of the study needed to do that.

VIII DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Each 100ml of the Icodextrin peritoneal dialysis solution contains 7.5g of Icodextrin. For each 2L long-dwell dialysis, 150 g of Icodextrin would be given. Of this 30-40% is absorbed depending on the duration of the long-dwell (12±2hours generally for CAPD). For 2.5L , 187.5g of Icodextrin would be given. Since efficacy was demonstrated for both 2L and 2.5L bag sizes and no dose-related toxicity was identified, the selection of what dose to give a particular patient can be based on clinical judgment.

Concerning efficacy relevant to the duration of the long-dwell, in MIDAS 8 hour dwells were used during weeks 3,12 and 20, while 12 hour dwells were used during weeks 4, 13 and 21. A 14±2 hours long-dwell time was used in Pro-Renal, and 12±4 hours was used for study 130. The glucose concentrations used in MIDAS were “weak”, i.e. 1.36% glucose, or “medium” or “strong”, i.e. 2.27 or 3.86% glucose respectively.

The comparative results were provided as follows:

Table 8: Repeated Measures Analyses of Mean Change in Net Ultrafiltration for the Long Dwell Exchange

Study	MLIB/001 (MIDAS)				RD-97-CA-130	PRO-RENAL-REG-035
	8-hr Dwell		12-hr Dwell		12 ± 4 hr Dwell	14 ± 2 hr Dwell
	1.5% Dextrose versus Extraneal	2.5/4.25% Dextrose versus Extraneal	1.5% Dextrose versus Extraneal	2.5/4.25% Dextrose versus Extraneal	2.5% Dextrose versus Extraneal	2.5% Dextrose versus Extraneal
Extraneal Adjusted Mean Change*	430	-200	479	-128	295	442
Dextrose Adjusted Mean Change*	107	-86	40	-184	70	2
Difference (Extraneal – Dextrose) for Change	322	-114	439	56	225	439
Std Error of Difference	53	61	56	75	51	67
Lower 90% Confidence Bound Difference	234	-216	346	-68	141	328
Upper 90% Confidence Bound Difference	411	-12	532	181	308	551
p-value**	<0.001	0.066	<0.001	0.435	<0.001	<0.001

* The adjusted mean changes from the repeated measures analysis of covariance, with Baseline values as the covariate, for each treatment group. A 90% confidence interval was constructed around the difference between Extraneal and dextrose.

** This p-value is from the two-sided test for treatment differences using the repeated measures analysis of covariance.
Reference: Appendix 2 Summary Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1, 5.5.1, and 5.6.1

Interpolating between trials it can be inferred that duration of the long-dwell does not much affect the net ultrafiltration benefit of Icodextrin versus 1.5% or 2.5% Dextrose.

Since the proposed market image of Icodextrin will include only the PD-2 electrolyte solution with contains 25.7mg/100ml calcium chloride, those patients who are taking Dextrose with PD-4 solution containing 18.3mg/100ml calcium chloride will be given the slightly higher calcium dose for the long-dwell. No case has been identified where this was associated with an adverse reaction. However, since a particular patient may be affected by the higher calcium dose, physician’s should be informed that use of Icodextrin for the long-dwell will include the slightly higher calcium dose as well.

IX. USE IN SPECIAL POPULATIONS

No children have been studied.

Analyses of the studies by age, Caucasian or Black race, gender, diabetic status, and hypertension have been carried out. All showed a similar direction of net ultrafiltration benefit compared to the total randomized population. Concerning Asian or Hispanic patients, too few were included to draw meaningful conclusions about efficacy or safety.

X. CONCLUSIONS and RECOMMENDATIONS:

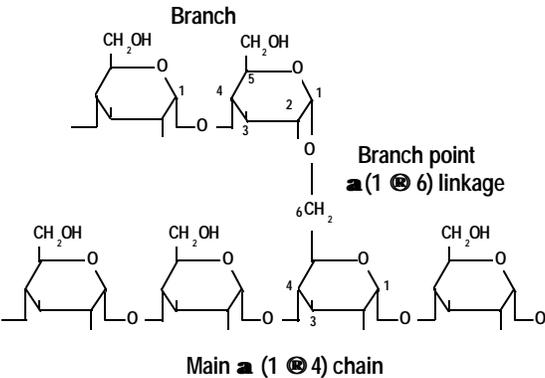
Icodextrin is an effective peritoneal dialysis drug based on historical expectations of patient outcome without it. It is more effective than 1.5% and 2.5% Dextrose in net ultrafiltration during the log-dwell dialysis period, but it has not been shown in the studies provided to provide a clinical benefit. However, it would be useful to have an alternative dialysis drug available for patients not adequately responding to their current regimen.

From a safety perspective, the mortality results in study 131 remain a concern. While this might be due to chance, it would be advisable to repeat that study. In addition to the mortality results, other findings such as rash and the laboratory abnormalities associated with the drug should be noted in the labeling.

Therefore, approval is recommended for the treatment of ESRD patients undergoing CAPD or APD during the single daily long-dwell 8-16 hours periods for those not adequately responding to their current regimen. A phase 4 commitment to repeat a mortality study similar to study 131.

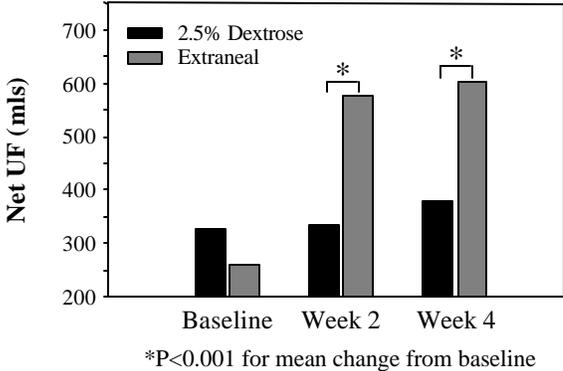
XI. LABELING

The sponsor's draft labeling with additional comments on the medical sections follow.

Package Insert Sections	VOL	Medical Reviewer Comments																																	
<p>EXTRANEAL™ (7.5% Icodextrin) Peritoneal Dialysis Solution</p> <p>DESCRIPTION EXTRANEAL™ (7.5% 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 alpha (1-6) glucosidic bonds with a weight average molecular weight between 12,000 and 20,000 Daltons and a number average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of icodextrin is:</p> <div style="text-align: center;">  <p>The diagram illustrates the structure of icodextrin. It features a horizontal 'Main α (1 → 4) chain' of four glucose units. A 'Branch point α (1 → 6) linkage' connects the C6 of the third unit in the main chain to the C1 of a 'Branch' consisting of two more glucose units. Each glucose unit is shown in its cyclic form with a CH₂OH group at the C2 position. Carbons are numbered 1 through 6 on each ring.</p> </div> <p>Each 1 liter of Extraneal contains: Electrolyte content per 1 liter:</p> <table border="0" style="width: 100%;"> <tr> <td style="width: 30%;">Icodextrin</td> <td style="width: 30%;">75.0 g</td> <td style="width: 40%;"></td> </tr> <tr> <td>Sodium Chloride</td> <td>5.4 g</td> <td></td> </tr> <tr> <td>Sodium Lactate</td> <td>4.5 g</td> <td></td> </tr> <tr> <td>Calcium Chloride</td> <td>257 mg</td> <td></td> </tr> <tr> <td>Magnesium Chloride</td> <td>51 mg</td> <td></td> </tr> <tr> <td colspan="3"> </td> </tr> <tr> <td> Sodium</td> <td>132 mEq/l</td> <td></td> </tr> <tr> <td> Calcium</td> <td>3.5 mEq/l</td> <td></td> </tr> <tr> <td> Magnesium</td> <td>0.5 mEq/l</td> <td></td> </tr> <tr> <td> Chloride</td> <td>96 mEq/l</td> <td></td> </tr> <tr> <td> Lactate</td> <td>40 mEq/l</td> <td></td> </tr> </table> <p>Water for Injection, USP qs HCl/NaOH may have been used to adjust pH Extraneal contains no bacteriostatic or antimicrobial agents. Theoretical osmolarity: 285-288 mOsm/L; pH=5.2</p>	Icodextrin	75.0 g		Sodium Chloride	5.4 g		Sodium Lactate	4.5 g		Calcium Chloride	257 mg		Magnesium Chloride	51 mg					Sodium	132 mEq/l		Calcium	3.5 mEq/l		Magnesium	0.5 mEq/l		Chloride	96 mEq/l		Lactate	40 mEq/l		<p>1.2</p> <p>1.2</p> <p>1.2</p> <p>1.3</p> <p>1.2</p>	
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Lactate	40 mEq/l																																		
<p>Extraneal is available for intraperitoneal administration only as a sterile, nonpyrogenic, clear solution in 1.5 L, 2.0 L and 2.5 L Ambu-Flex III™ and Ultrabag™ containers. The container systems are composed of polyvinyl chloride.</p>	<p>1.2</p>																																		

Package Insert Sections	VOL	Medical Reviewer Comments
	<u>CLINICAL PHARMACOLOGY</u>	
<p><u>Mechanism of Action</u></p> <p>Extraneal is an isosmotic peritoneal dialysis solution containing glucose polymers (icodextrin) as the primary osmotic agent. Icodextrin functions as a colloid osmotic agent to achieve sustained ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in a steady rate of transcapillary ultrafiltration throughout the dwell. Extraneal also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.</p>	1.13	
<p><u>Pharmacokinetics of Icodextrin</u></p> <p><i>Absorption</i></p> <p>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 40.1% (60.2 g) of the instilled icodextrin was absorbed from the peritoneal solution during a 12-hour dwell.</p>	1.25	
<p><u>Plasma levels of icodextrin rose during the dwell and declined after the dwell was drained, consistent with a one-compartment model with zero order absorption and first order elimination. Peak plasma concentrations (median $C_{peak} = 2.23$ g/L) were observed at the end of the long dwell exchange (median $T_{max} = 12.7$ hours) with plasma levels returning to baseline values within 3 to 7 days following cessation of icodextrin administration. Icodextrin had a plasma half-life of 14.7 hours and a median clearance rate of 1.08 L/hr.</u></p>	1.25	
<p><u>The mean steady-state plasma levels of icodextrin predicted from the above parameters (5.26 g/L) corresponded very closely to the stable plasma icodextrin values observed during long-term administration.</u></p>	1.25 1.38	
<p>In multidose studies, steady-state levels of icodextrin were achieved within one week and returned to baseline within one week after discontinuation of Extraneal use.</p>	1.54	

Package Insert Sections		
	VOL	Medical Reviewer Comments
<p>Metabolism</p> <p>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.</p>	1.25	<i>Icodextrin is not completely metabolized. Provide data on steady-state blood levels.</i>
Steady-state plasma levels of icodextrin metabolites were achieved within one week and stable plasma levels were observed during long-term administration.	1.38	
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.	1.25	
<p>Elimination</p> <p>Icodextrin undergoes renal elimination in direct proportion to the level of residual renal function (r=0.824 vs creatinine clearance, p<0.01). In nine patients with residual renal function (mean creatinine clearance: 5.0 ± 1.5 ml/min), the average daily urinary excretion of icodextrin was 473 ± 77 mg per ml of creatinine clearance. Diffusion of the smaller icodextrin metabolites from plasma into the peritoneal cavity is also possible after systemic absorption and metabolism of icodextrin.</p>	1.25	
<p>Special Populations</p> <p>Geriatrics</p> <p>In clinical studies of Extraneal in which plasma levels of icodextrin and its metabolites were measured, 95 patients were aged 65 and older. No apparent differences in plasma levels were observed in patients aged 65 and older as compared to patients under age 65.</p>	1.71 1.93	
<p>Gender and Race</p> <p>Although no specific studies were conducted to evaluate the differences between gender and race within the clinical trial data for icodextrin, no known differences have been detected.</p>	1.31 1.54	<i>If no PK or PD studies to investigate gender or race differences were done, we cannot conclude that we know there are no differences.</i>
<p>Pharmacodynamics and Clinical Effects</p> <p>Extraneal has demonstrated efficacy as a peritoneal dialysis solution in clinical trials of approximately 400 patients studied with end-stage renal disease (ESRD).</p>	1.69	

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><i>Ultrafiltration, Urea and Creatinine Clearance, Negative Net Ultrafiltration</i></p> <p>In active controlled trials from one to six months in duration, Extraneal used once daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or ambulatory peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration and clearances when compared with 2.5% Dextrose solutions.</p>	<p>1.31</p> <p>1.54</p> <p>1.57</p>
<p>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 for the Extraneal group compared to the 2.5% Dextrose group when evaluated at weeks 2 and 4 (Figure 1).</p> <p>Figure 1 - Mean Net Ultrafiltration for the Overnight Dwell (RD-97-CA-130)</p>  <p>In 39 APD patients randomized to Extraneal or 2.5% Dextrose solution for the long, daytime dwell (10-17 hrs) for three months, the average net ultrafiltration reported during the treatment period was 278 ± 43 ml for the Extraneal group and -138 ± 81 ml for the Dextrose group (P<0.001).</p>	<p>1.31</p> <p>1.54</p>	

Package Insert Sections		VOL	Medical Reviewer Comments																								
<p>Mean creatinine and urea nitrogen clearances were significantly greater for Extraneal as compared with 2.5% Dextrose in CAPD patients at weeks 2 and 4 (Figure 2) and in APD patients at weeks 6 and 12 (P<0.001).</p> <p>Figure 2 – Mean Creatinine and Urea Clearance for the Overnight Dwell (RD-97-CA-130)</p> <table border="1"> <caption>Estimated data for Figure 2</caption> <thead> <tr> <th rowspan="2">Time Point</th> <th colspan="2">Creatinine Clearance (mL/min)</th> <th colspan="2">Urea Clearance</th> </tr> <tr> <th>2.5% Dextrose</th> <th>Extraneal</th> <th>2.5% Dextrose</th> <th>Extraneal</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>~3.4</td> <td>~3.4</td> <td>~4.2</td> <td>~4.2</td> </tr> <tr> <td>Week 2</td> <td>~3.4</td> <td>~4.1*</td> <td>~4.1</td> <td>~4.6*</td> </tr> <tr> <td>Week 4</td> <td>~3.5</td> <td>~4.0*</td> <td>~4.1</td> <td>~4.5*</td> </tr> </tbody> </table> <p>*P<0.001 for mean change from baseline (Creatinine Clearance); *P<0.01 for mean change from baseline (Urea Clearance)</p>		Time Point	Creatinine Clearance (mL/min)		Urea Clearance		2.5% Dextrose	Extraneal	2.5% Dextrose	Extraneal	Baseline	~3.4	~3.4	~4.2	~4.2	Week 2	~3.4	~4.1*	~4.1	~4.6*	Week 4	~3.5	~4.0*	~4.1	~4.5*	<p>1.31 1.54</p>	<p><i>What of comparisons to 1.5% and 4.5% Dextrose?</i></p>
Time Point	Creatinine Clearance (mL/min)		Urea Clearance																								
	2.5% Dextrose	Extraneal	2.5% Dextrose	Extraneal																							
Baseline	~3.4	~3.4	~4.2	~4.2																							
Week 2	~3.4	~4.1*	~4.1	~4.6*																							
Week 4	~3.5	~4.0*	~4.1	~4.5*																							
<p>Extraneal resulted in a significant decrease in the percentage of patients with negative net UF during long peritoneal dialysis dwells (10-17 hrs). When compared to 2.5% Dextrose solution, the percentage of patients who were unable to achieve positive or zero ultrafiltration was significantly lower for patients using Extraneal for the long dwell in both CAPD and APD.</p>		<p>1.31 1.54 1.57</p>																									

Package Insert Sections	VOL	Medical Reviewer Comments
	<p>Long-term (12 month) Use A randomized 12-month safety study (N=287) evaluated a single daily exchange of Extraneal for the 8 to 16-hour dwell in ESRD patients using CAPD or APD. One hundred seventy-five (175) patients were randomized to Extraneal and 112 patients to 2.5% Dextrose.</p> <p><i>Body Weight:</i> Long-term use (12 months) of Extraneal resulted in maintenance of stable body weight compared to a mean weight gain of 2.3 kg in the 2.5% Dextrose group. The lack of weight gain observed in the Extraneal group may be related to a reduction in the glucose load during long dwells.</p> <p><i>Fluid Balance:</i> Significantly fewer patients receiving Extraneal reported edema at Weeks 26 and 39 during the 12-month study when compared to patients on 2.5% Dextrose (20% vs 35%). Overall, 17.9% of patients in the control group reported peripheral edema as compared to 6.3 % in the Extraneal group.</p> <p><i>Peritoneal Membrane Transport Characteristics:</i> After one year of treatment with Extraneal during the long dwell exchange, there were no differences in membrane transport characteristics for urea and creatinine. There was a slight increase in the mass transfer area coefficient (MTAC) for glucose at one year, but it was not different from the change in MTAC in patients receiving treatment with 2.5% Dextrose solution for the long dwell.</p> <p><i>Quality of Life:</i> Quality of life in the 12-month study was assessed by the Kidney Disease Quality of Life (KDQoL) evaluation. When asked to evaluate their general health at study completion, versus their baseline assessment, a significantly greater percentage of patients in the Extraneal group (30%) responded that their health was “much better now than one year ago” compared to the Control group (4%) (p<0.03).</p>	<p>1.38</p> <p>1.38</p> <p>1.38</p> <p>1.38</p>
<p><u>INDICATIONS AND USAGE</u> Extraneal is indicated for a single daily exchange for the long (8 – 16 hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of chronic renal failure.</p> <p>In clinical studies, Extraneal demonstrated enhanced ultrafiltration and creatinine and urea clearances when compared to 2.5% Dextrose solutions. The percentage of patients with net negative ultrafiltration was significantly reduced with Extraneal compared to 2.5% Dextrose (See CLINICAL PHARMACOLOGY –Pharmacodynamics and Clinical Effects).</p>	<p>1.38</p>	<p><i>Add: in patients not adequately responding to their current dialysis regimen. Delete second paragraph since clinical benefit was not established in the studies.</i></p>
<p><u>CONTRAINDICATIONS</u> Extraneal is contraindicated in patients with a known allergy to cornstarch or icodextrin or in patients with glycogen storage disease.</p>		
<p><u>WARNINGS</u> Not for intravenous injection.</p>		

Package Insert Sections		
	VOL	Medical Reviewer Comments
<p><u>PRECAUTIONS</u></p> <p><u>General</u></p> <p><i>Peritoneal Dialysis Related</i></p> <p>All peritoneal dialysis solutions, including Extraneal, should be used with caution in patients with a history of abdominal surgery within thirty 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.</p> <p>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.</p>		
<p>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.</p>		
<p>Significant losses of protein, amino acids, and water-soluble vitamins may occur during peritoneal dialysis. The patient's nutritional status should be monitored and replacement therapy provided as necessary.</p> <p>Extraneal solution should be inspected for clarity, absence of particulate matter and container integrity. Solutions, which are cloudy, contain particulate matter, or evidence of leakage should not be used.</p> <p>Treatment should be initiated and monitored under the supervision of a physician knowledgeable in the management of patients with renal failure.</p>		<p><i>Add: In patients with hypercalcemia, particularly in those on low calcium peritoneal dialysis solutions, consideration should be given to the fact that Icodextrin peritoneal dialysis solution is not provided with low calcium electrolyte solution.</i></p>
<p><i>Insulin dependent diabetes mellitus</i></p> <p>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 (<i>See Drug /Laboratory Test Interactions</i>).</p>		

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><u>Information for Patients</u> <u>Patients should be instructed to inspect each container of Extraneal solution for clarity, particulate matter, color and integrity of the container prior to use. Solutions should not be used if they are cloudy, discolored, contain visible particulate matter or if they have evidence of leaking containers.</u></p> <p>Aseptic technique should be employed throughout the procedure.</p> <p>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 overwrap. 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. (<i>See Directions for Use</i>)</p> <p>Additional information for patients is provided at the end of the labeling.</p>	
<p><u>Laboratory Tests</u> <i>Serum Electrolytes</i></p> <p>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 regarded as clinically unimportant, monitoring of the patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.</p> <p>Extraneal does not contain potassium. Evaluation of serum potassium should be made prior to administering potassium chloride to the patient.</p>	<p>1.31 1.38 1.54</p>	
<p><i>Alkaline Phosphatase</i></p> <p>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.</p>	<p>1.31 1.38 1.54</p>	<p><i>There have been individual cases where elevated alkaline phosphatase has been associated with elevated AST(SGOT), but neither elevation was thought to be causally related to the drug.</i></p>
<p><u>Drug Interactions</u> <i>General</i></p> <p>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, plasma levels of calcium, potassium and magnesium must be carefully monitored.</p>		

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><i>Insulin</i></p> <p>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 (<i>See Drug /Laboratory Test Interactions</i>) of blood glucose should be performed when initiating Extraneal in diabetic patients and insulin dosage should be adjusted if needed (<i>See Precautions</i>).</p>	<p>1.30</p> <p>1.21</p>
<p><i>Heparin</i></p> <p>No human drug interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with Extraneal.</p>	<p>1.21</p>	
<p><i>Antibiotics</i></p> <p>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. (<i>See Dosage and Administration</i>)</p>	<p>1.22</p> <p>1.21</p> <p>1.22</p>	
<p><u>Drug/Laboratory Test Interactions</u></p> <p><i>Blood Glucose</i></p> <p>Blood glucose measurement must be done with a glucose specific method to prevent maltose interference with test results. Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) based methods should not be used.</p>	<p>1.22</p>	
<p><i>Serum Amylase</i></p> <p>An apparent decrease in serum amylase activity has been observed in patients 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.</p>	<p>1.22</p>	
<p>Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Icodextrin did not demonstrate evidence of mutagenic potential in <i>in vitro</i> or <i>in vivo</i> studies performed. 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 that is generally regarded as safe.</p>	<p>1.11</p>	
<p>A preliminary fertility study in rats revealed slightly low epididymal weights in parental males in the high dose group (1.5 g/kg/day), 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. Studies on the effects of icodextrin on male and female fertility have not been performed.</p>	<p>1.12</p>	

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><u>Pregnancy</u> <i>Pregnancy Category C</i> Complete animal reproduction studies 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.</p>	
<p>A preliminary study of the effects of icodextrin on the fertility and pregnancy in rats demonstrated no effects of treatment with icodextrin on mating performance, fertility, litter response, embryo-fetal survival, or fetal growth and development.</p>	1.12	
<p><u>Nursing Mothers</u> 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.</p>		
<p><u>Pediatric Use</u> Safety and effectiveness in pediatric patients have not been established.</p>		
<p><u>Geriatric Use</u> No formal studies were specifically carried out in the geriatric population. However, approximately 25% of the patients in clinical studies of Extraneal were age 65 or older, with ~ 4% of 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.</p>	1.69 1.71	
<p><u>ADVERSE REACTIONS</u></p> <p>Adverse Reactions from Clinical Trials Significance of Adverse Reaction Data Obtained from Clinical Trials 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.</p>		
<p>Extraneal was studied in controlled clinical trials of 366 patients with end-stage renal disease, including 60 patients exposed for 6 months and 155 patients exposed for one year. The population was 18-93 years of age, 56% male and 44% female, 73% Caucasian, 18% Black, 4% Asian, 3% Hispanic and included patients with the following comorbid conditions: 26.8% diabetes, 49.3% hypertension and 23.1% hypertensive nephropathy. All patients received a single daily exchange of Extraneal for the long dwell (8-16 hours).</p>	1.71	<i>N=493 patients in ISS. Update.</i>

Package Insert Sections	VOL	Medical Reviewer Comments
	<p>Rash was the most frequently occurring icodextrin-related adverse event (5.5%, Extraneal; 1.7% Control). A listing of adverse events reported in these same clinical studies, regardless of causality, occurring in $\geq 5\%$ of patients is presented in Table 1.</p>	<p>1.71 1.72</p>
<p>Additional adverse reactions that were possibly, probably or definitely related to Extraneal with an incidence of less than 5% within each body system were as follows: <i>Body as a Whole</i> - neck pain, PD catheter dysfunction, facial edema, bloody effluent; <i>Cardiovascular</i> - postural hypertension, tachycardia, cardiovascular disease, syncope, cerebrovascular accident, palpitations; <i>Hematologic and Lymphatic</i> - leukocytosis, eosinophilia; <i>Digestive</i> - anorexia, abnormal liver function, constipation, gastrointestinal disorder, flatulence, gastritis, intestinal obstruction, stomach ulcer; <i>Metabolic and Nutrition</i> - dehydration, hypovolemia, hypochloremia, hypomagnesemia, weight increase, increase alkaline phosphatase, hyponatremia, hypoglycemia, increase SGOT, increase SGPT, decreased weight, decreased ultrafiltration, increase creatinine; <i>Musculoskeletal</i> - myalgia, cramps, leg cramping, bone pain; <i>Nervous</i> - paresthesia, dry mouth, anxiety, hyperkinesia, nervousness, abnormal thinking; <i>Respiratory</i> - lung disorder, lung edema, hiccup; <i>Skin</i> - exfoliative dermatitis, nail disorder, psoriasis, macular-papular rash, eczema, furunculosis, bulbar vesicular rash, skin discoloration, dry skin, skin ulcer, urticaria; <i>Special Senses</i> - loss of taste; <i>Urogenital</i> - kidney pain.</p>	<p>1.72</p>	<p><i>Use data whether or not considered related.</i></p>

Package Insert Sections		VOL	Medical Reviewer Comments
Table 1 - Adverse Experiences in ≥ 5 % of Patients			
	Extraneal N = 366 Control N=347		<i>Update</i>
	N (%) N (%)	171	
Body in General		172	
Peritonitis	130 (26.4) 88 (25.4)		
Exit Site Infection	73 (14.8) 58 (16.7)		
Pain	48 (9.7) 43 (12.4)		
Headache	43 (8.7) 23 (6.6)		
Pain Abdominal	39 (7.9) 20 (5.8)		
Flu Syndrome	35 (7.1) 21 (6.1)		
Injury Accidental	31 (6.3) 14 (4.0)		81

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><i>Peritoneal Dialysis Related</i></p> <p>Adverse events common to the treatment modality of peritoneal dialysis including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain were observed at a similar frequency with Extraneal and Controls (<i>See Precautions</i>).</p>	
<p><i>Changes in Alkaline Phosphatase and Serum Electrolytes</i></p> <p>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.</p>	<p>1.31 1.38 1.54</p>	
<p>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 regarded as clinically unimportant, monitoring of the patients serum electrolyte levels as part of routine blood chemistry testing is recommended.</p>	<p>1.31 1.38 1.54</p>	
<p><u>DRUG ABUSE AND DEPENDENCE</u></p> <p>There has been no observed potential of drug abuse or dependence with Extraneal.</p>		
<p><u>OVERDOSAGE</u></p> <p>No data is available on experiences of overdosage with Extraneal. Overdosage of Extraneal may result in higher levels of serum icodextrin and metabolites. It is unknown what symptoms may be caused from exposure in excess of those observed in clinical trials. In the event of overdosage with Extraneal, continued peritoneal dialysis with glucose-based solutions should be provided.</p>		

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><u>DOSAGE AND ADMINISTRATION</u></p> <p>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.</p> <p>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 over or under hydration and potentially severe consequences including congestive heart failure, volume depletion and hypovolemic shock.</p> <p>Aseptic technique should be used throughout the peritoneal dialysis procedure.</p> <p>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. 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. (<i>See Directions for Use</i>)</p> <p>Extraneal should be administered over a period of 10-20 minutes at a rate that is comfortable for the patient.</p> <p>Parenteral drug products, including Extraneal, should be visually inspected for particulate matter, leakage and discoloration prior to use. Should these be present, discard product; do not use.</p> <p>Following use, the drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of an infection.</p>	1.4
<p><u>Addition of Insulin</u></p> <p>Addition of insulin to Extraneal was evaluated in 6 insulin dependent diabetic patients undergoing CAPD for end stage renal disease. No interference of Extraneal on insulin absorption from the peritoneal cavity or on insulin's ability to control on blood glucose was observed (<i>See Drug /Laboratory Test Interactions</i>). Appropriate monitoring of blood glucose should be performed when initiating Extraneal in diabetic patients and insulin dosage adjusted if needed (<i>See Precautions</i>).</p>	1.30 1.21	
<p><u>Addition of Heparin</u></p> <p><u>No human drug interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with Extraneal.</u></p>	1.21	

Package Insert Sections	VOL	Medical Reviewer Comments
	<p><i>Addition of Antibiotics</i> 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/flucoxillin, ceftazidime, gentamicin, and amphotericin. Patients undergoing peritoneal dialysis should be under careful supervision of a physician experienced in the treatment 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. Training materials are available from Baxter Healthcare Corporation, Deerfield, IL 60015, USA.</p>	<p>1.22 1.21 1.22</p>
<p>Directions for Use For complete CAPD and APD system preparation, see directions accompanying ancillary Aseptic technique should be used.</p>		
<p><i>Warming</i> 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. 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.</p>	1.4	
<p><i>To Open</i> To open, tear the over wrap 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.</p>		
<p><i>Inspect for Container Integrity</i> Inspect the container for signs of leakage and check for minute leaks by squeezing the container firmly.</p>		
<p><i>Adding Medications</i> 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.</p> <ol style="list-style-type: none"> 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. 		
<p><i>Preparation for Administration</i></p> <ol style="list-style-type: none"> 1. Place Extraneal on flat surface or suspend from support (depending on ancillary equipment). 2. Remove protector from outlet port on container. 3. Attach solution transfer set. Refer to complete instructions with ancillary equipment or transfer set. 4. Discard any unused portion. 		

