CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY &BIOPHARMACEUTICS REVIEW

NDA:21,321	**Submission Date:**	August 31, 2001
Drug Name:	Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution	
Formulation:	Solution	
Applicant:	Baxter Healthcare Corporation	
Submission:	Original NDA amendment	
Reviewer:	Elena V. Mishina, Ph.D.	

Preamble/Background:

Extraneal (7.5% icodextrin) is proposed as a solution for long dwell exchange in peritoneal dialysis (PD), for the treatment of chronic renal failure. Extraneal is designed to maintain the gradient over long-dwell periods of peritoneal dialysis, and therefore, increase the efficiency of dialysis. Icodextrin is a soluble, polydispersed, high molecular weight glucose polymer isolated by fractionation of hydrolyzed cornstarch and is administered with electrolytes in sterile 2.0-2.5 L solution.
Cardio-Renal Advisory Committee for Extraneal on August 9, 2001 requested the sponsor to submit box-plot analyses of blood pressure and analyses overlayed with patient deaths for the 12 month clinical study RD-97-CA-131. In this amendment, the sponsor additionally provided the revised draft of the Package Insert.

Comments:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the revised draft of the Package Insert for Extraneal and found it acceptable.

RECOMMENDATION

The revised draft of the Package Insert for Extraneal is acceptable from the point of view of the Office of Clinical Pharmacology and Biopharmaceutics. No action is necessary.

/S/ Date

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 21,321, MehulM, MishinaE, HFD 110 BIOPHARM

Package Insert Sections	Comments

24 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Elena Mishina
9/24/01 01:58:06 PM
BIOPHARMACEUTICS

Patrick Marroum
9/24/01 04:20:20 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**21,321**	**Relevant IND:**	—
Submission Date:	December 22, 2000		
Drug Name:	Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution		
Formulation:	Solution		
Applicant:	Baxter Healthcare Corporation		
Submission:	Original NDA, orphan drug designation		
Reviewer:	Elena V. Mishina, Ph.D.		

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Table of Review Status of the Submitted Studies

Study	Description	Reviewed	Reason if not reviewed
RD-99-CA-060	Single dose PK	yes	
RD-97-CA-130	Safety & efficacy in CAPD	yes	
RD-97-CA-131	Safety & efficacy in PD	yes	
PRO-RENAL-REG-035	Safety & efficacy in APD	yes	
ML/IB/015 (MIDAS)	Steady state icodextrin levels with stoping treatment	no	assay
ML/IB/001 (MIDAS)	CAPD trial	no	assay
ML/IB/004 (MIDAS2)	CAPD trial - 2	no	assay
ML/IB/020 (DELIA)	APD trial	no	assay
ML/IB/011 (DIANA)	Biocompatibility of glucose polymer solution in APD	no	assay
MTR(F)	Formulation feasibility	no	Formulation has not been used in clinic
MTR(1)-MTR(7)	Formulation feasibility	no	Formulation has not been used in clinic
RD-94-RE-067	Assay validation in dialysate & plasma	yes	
TP06BC99376	Evaluation of two assay methods	yes	
10318	Assay validation	yes	
RD-RE-B-013	Metabolites assay in plasma	yes	
RD-95-RE-134	Assay validation	yes	
RD-98-RE-010	Assay validation	yes	
RD-94-RE-074	Assay validation	yes	
RD-96-PD-041	Drug compatibility	yes	
RD-96-PD-067	Compatibility with insulin in vitro	yes	
RD-96-PD-038	Compatibility with cefazolin & cefrazidime	yes	
ML/IB/002	Addition of insulin to CAPD in vivo	yes	
REP-NIV-RE-366	Interference of glucose assay with enzymatic methods	yes	
91/3546/MB	MIC of antibiotics in vitro	yes	
RD-96-PD-135	Compatibility of netilmycin	yes	
11360	Amylase activity	yes	

RECOMMENDATION

The NDA 21,321 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. Please forward the comments below and labeling recommendations to the sponsor as appropriate.

COMMENTS

1. The assay used by the sponsor to measure the total icodextrin concentrations in all matrixes is lacking specificity. Quality control samples are not provided in each of the submitted studies. Therefore, it is impossible to evaluate the precision and accuracy of the assay methods used by the sponsor.

2. Icodextrin and its metabolites concentrations are measured in plasma, urine and spent dialysate in the studies after the single 12 hours dwell and at steady state. Icodextrin pharmacokinetics profiles in the peritoneal cavity decline with zero-order rate constant. The model proposed by the sponsor to describe plasma kinetics of total icodextrin is not reliable due to the lack of assay specificity and measurements referring to the sum of glucose polymers. Thus the calculated parameters for total icodextrin should not be included in the Package insert.

3. The sponsor did not make an attempt to describe the pharmacokinetic characteristics of icodextrin metabolites.

4. Net absorption of icodextrin to the systemic circulation after the single 12 hours dwell and during the chronic automated PD procedures was similar, about 40%. Peak plasma total icodextrtin and its degradation products concentrations were between and g/L through all studies. Therefore, the sponsor properly concluded that the duration and mode of PD procedures do not influence the systemic exposure to total icodextrin.

OCPB Briefing held on July 10, 2001. Attendees were: Mehul Mehta, John Hunt, Arzu Selen, Chandra Sahajwala, Patrick Marroum, Nhi Nguen, Bukhard Jansen, Shiew-Mei Huang, Ike Lee.

/S/

_______________________ Date_______________

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: MehulM, MishinaE, HFD 110 BIOPHARM

EXECUTIVE SUMMARY:

Extraneal (7.5% icodextrin) is proposed as a solution for long dwell exchange in peritoneal dialysis (PD), for the treatment of chronic renal failure. PD is a procedure for the management of patients with chronic renal failure who require maintenance dialysis. The principal osmotic agent for PD is dextrose (D-glucose monohydrate). Its use is complicated by its rapid absorption from the peritoneal cavity and a decrease of osmotic gradient during the long dwells followed by a decrease of the ultrafiltration rate. Extraneal is designed to maintain the gradient over long-dwell periods of peritoneal dialysis, and therefore, increase the efficiency of dialysis. Icodextrin is a soluble, polydispersed, high molecular weight glucose polymer isolated by fractionation of hydrolyzed corn starch and is administered with electrolytes in sterile 2.0-2.5 L solution.

Orphan Drug Designation was granted to the IND [redacted] Extraneal in 1996. After that, two Phase 3 safety and efficacy studies were conducted. Additionally, as requested by the Agency a Phase 1 pharmacokinetic study of icodextrin after single dose was performed.

There were 16 clinical pharmacology studies submitted with this NDA. These were one single dose, 8 multiple dose studies, and 7 feasibility and formulation studies. Of these studies, 4 were used to make Clinical Pharmacology and Biopharmaceutics recommendations. The early studies (MIDAS, DIANA, and DELIA) were found to be unacceptable due to assay issues. The feasibility and formulation studies (MTR) deal with the formulation development and are not related to the to-be-marketed formulation. Additionally, several reports of assay validation, drug compatibility and assay interference were submitted to the Agency and reviewed.

Three analytical methods were applied for the assay of different species. Total icodextrin was assayed in plasma, spent dialysate and urine by [redacted] Icodextrin metabolites were detected in blood, spent dialysate, and urine by [redacted] and in plasma and urine by [redacted]). All methods were properly validated for accuracy and precision. However, the last one was validated only for 3 metabolites of icodextrin, and the limit of detection was not reported. It was used in DIANA and DELIA studies. In the MIDAS studies, the method of assay of icodextrin and its metabolites used by the sponsor has not been specified. Therefore, the drug concentration results of these studies cannot be evaluated.

Since the sponsor used a nonspecific assay that quantitates not only icodextrin but the total sum of icodextrin and its metabolites no reliable estimates of the pharmacokinetic parameters of icodextrin and its metabolites could be calculated. Therefore, these parameters should not be reported in the Package Insert since they refer to the total exposure to icodextrin and its metabolites.

Icodextrin is metabolized by amylase, and therefore, it interferes with the quantitation of amylase activity. Because of the competitive interaction of icodextrin and the chromogenic substrate used in the amylase assay kit, the results of the amylase assay should be conservatively interpreted in patients using icodextrin.

The efficacy of peritoneal dialysis is assessed by its ability to remove solutes and fluid (clearance and ultrafiltration). Additionally, PD solutions manage the electrolyte and acid-base balance. Net ultrafiltration and creatinine and urea clearance obtained with icodextrin were superior to the same for dextrose solutions (1.5, 2.5, and 4.25%), studies RD-97-CA-130 and MIDAS. In 175 controlled automatic PD patients (CAPD) randomized to Extraneal or 2.5% dextrose solution for 8-15 hours overnight dwell for one month, mean net ultrafiltration was significantly greater ($p < 0.001$) for the Extraneal group when evaluated at weeks 2 and 4. The long-term use of icodextrin for long (12 hours dwell) was safe and effective (Studies RD-97-CA-131 and PRO-RENAL-REG-035).

PD solutions are administered parenterally into the peritoneal cavity, therefore, they are considered fully bioavailable immediately after instillation.

Absorption of icodextrin from the abdominal cavity follows zero-order kinetics with convective transport via peritoneal lymphatic pathways. After the single 12 hours dwell, a median of 40% of the instilled icodextrin was absorbed into plasma at a rate of 5 g/hr. The sponsor described the pharmacokinetics of total icodextrin in plasma with a one-compartmental model with zero order absorption. Half-life was estimated as 14.7 hours, and clearance was 1.08 L/hr. The data for total icodextrin show a more complex profile than a one-compartmental model. After multiple dwells, total icodextrin plasma concentrations achieve steady state at week 2, suggesting that the calculated icodextrin half-life was under estimated. The proposed assay for the total icodextrin is lacking specificity. Moreover, the parameters estimated from bulk measurement of the sum of glucose polymers could not be interpreted physiologically. Therefore, the values reported by the sponsor are not reliable. These parameters should not be cited in the Package insert.

Icodextrin is metabolized to glucose polymers of smaller degree of polymerization (eventually to maltose) by amylase. Polymers with degree of polymerization from 2 (DP2) to 7 (DP7) were detected in plasma and spent dialysate. As the various polymers undergo metabolism, the concentration of smaller polymers rise and those of the larger polymers decline. There is a progressive rise in the dialysate concentration of smaller polymers (DP2 to DP4) and a progressive decline of the larger polymers (DP5 to DP7). Some metabolism of icodextrin can occur in the peritoneal cavity as well as their diffusion from plasma. Icodextrin metabolism is not complete by 12 hours dwell, but after a single dwell, their concentrations in plasma reach pretreatment level within a few days. At steady-state mean plasma level of total icodextrin (icodextrin and its degradation products) was about 5 g/L, and 0.85, 0.81, 0.32, 0.036, 0.018 and 0.023 g/L for DP2, DP3, DP4, DP5, DP6, and DP7 metabolites, respectively.

Icodextrin is eliminated renally in direct proportion to the residual renal function. In nine patients with mean creatinine clearance of 5.0 ± 1.5 mL/min the average daily excretion of total icodextrin (icodextrin and its degradation products) was 473 ± 77 mg per mL of creatinine clearance.

Although clinical studies where icodextrin and its metabolite concentrations were measured were balanced for age, gender and race, the influence of these covariates on the icodextrin pharmacokinetics were not evaluated statistically. In study RD-97-CA-130, the influence of diabetic status-by-visit on the net ultrafiltration was marginally significant ($p=0.094$), however, the sample size was small to draw a general conclusion. Therefore, the conclusions about the differences in pharmacokinetics and pharmacodynamics of icodextrin in special populations cannot be made.

On some occasions, it is necessary to coadminister intraperitoneally with PD solution a variety of antibiotics, heparin, and insulin. Possible interaction of icodextrin with these drugs either alone or in combination with each other was studied. In vitro incubation of icodextrin up to 36 or 48 hours, does not change the minimum inhibitory concentration (MIC) of gentamicin vancomycin, cefazolin, ceftazidine. Insulin lost more than 10% of its potency. Heparin was fully compatible. Six diabetic patients were randomized in an open crossover study to receive dialysis with Extraneal or 1.5% dextrose for a single 6 hours dwell. Insulin was administered with a PD solution. Insulin levels in plasma and dialysate were similar in both arms, therefore, insulin could be added to Extraneal for diabetic patients with CAPD.

QUESTION BASED REVIEW

BACKGROUND:

Questions addressed in this section:

What are the mechanisms of peritoneal dialysis?
What are the disadvantages of use of glucose solutions for PD?
How the effect of peritoneal dialysis measured?

Peritoneal dialysis (PD) is a procedure for the management of patients with chronic renal failure who require maintenance dialysis. A sterile dialysis solution is administered intraperitoneally via an indwelling catheter. During the dwell, solutes, such as urea and creatinine, diffuse from capillaries in the peritoneal membrane and adjacent tissues into the dialysis solution. Simultaneously, water and solutes are driven across the peritoneal membrane due to an osmotic pressure gradient of the solution. At the end of dwell, the dialysis solution is drained from the peritoneal cavity thus removing toxins and excess of fluid, and fresh dialysis solution is administered. Except for the osmotic agent, solutions for dialysis includes electrolytes (sodium, chloride, calcium and magnesium) and a source of buffers (usually lactate) to help maintain acid-base status in patient with end stage of renal disease (ESRD).
For each patient, the number of exchanges, dwell time, volume of fluid, and concentrations of the osmotic agent may be adjusted individually. The exchange may be manual (CAPD) or performed automatically (APD). The principal osmotic agent used in most PD contains 1.5, 2.5, or 4.25% dextrose (equivalent to 1.36, 2.27, and 3.86% of anhydrous glucose, respectively). It acts as a crystalloid osmotic agent to effect fluid removal or ultrafiltration (UF).

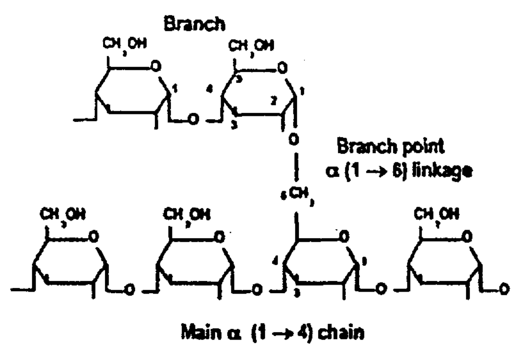
The use of dextrose is complicated by its rapid absorption from the peritoneal cavity. Upon initial instillation, the osmotic gradient is maximal then it decreases due to glucose absorption. For short-term (2-6 hours) dwell, this effect is not important but for long-time (overnight) dwells it often leads to net fluid reabsorption (negative ultrafiltration) rather then fluid removal at the end of the dwell. Additionally, the use of dextrose leads to an increase in the systemic glucose load, which may cause weight gain and metabolic abnormalities including hyperlipidemia and hyperinsulinemia.
These problems can be overcome with the use of dextrose polymers in PD solution. Glucose polymers act by a colloid osmosis: fluid flows across the membrane permeable to small solutes in the direction of the relative excess of impermeable large solutes, rather than along the osmolality gradient.

The efficacy of PD is determined by its ability to remove solutes (clearance) and fluids (ultrafiltration). Solute removal depends on the solute's diffusive capacity, the concentration gradient across the membrane and the patient specific characteristics of the peritoneal membrane. Solute clearance is determined by the molecular weight of the solute, the membrane permeability characteristics, the volume of the instilled fluid and the length of the dwell. The solute continues to diffuse into the dialysis solution until the concentration of the solute in the dialysate approaches that of the blood. Ultrafiltration is governed by the osmotic pressure gradient and dependent on the concentration of the osmotic agent in the dialysis solution. Additionally, it depends on the permeability characteristics of the osmotic agent and peritoneal membrane. Low molecular weight osmotic agent can be easily absorbed, which leads to a decline in the rate of ultrafiltration. The absorption of PD solution depends on its diffusive capacity (for low molecular weight components) and the rate of convective transport primarily by the lymphatics (for higher molecular weight components or colloid). The rate of fluid uptake into the lymphatic system is relatively constant and independent of the solution composition.

What are the chemical and composition characteristics of Extraneal?

Extraneal is a PD solution containing 7.5% (w/v) icodextrin as an osmotic agent.
Icodextrin is a glucose polymer, which act as a colloid osmotic agent and can replace glucose in peritoneal dialysis. The advantages to use solutions with glucose polymers are in their ability to introduce transcapillary ultrafiltration even though they are not hypertonic and in the low absorption of glucose into the systemic circulation.
Extraneal differs from the commonly used Dianeal for PD only by the osmotic agent. Icodextrin is a soluble, polydispersed, high molecular weight polymer of glucose isolated by the fractionation of hydrolyzed cornstarch. A representation of the structure of icodextrin is shown in Figure 1.

Figure 1. Representation of the Structure of Icodextrin



In the mixture, the polymers have various chain lengths. The average molecular weight of a polymer, Mn is described as follows:

$$M_n = \frac{\sum_i n_i M_i}{n}$$

where M is a molecular weight of each polymer and n is the number of polymers.
The weight average, Mw is

$$M_W = \frac{\sum_i n_i \cdot M_i}{n \cdot \sum_i M_i}$$

where n is a number of molecules with each molecular weight Mi.
For Icodextrin, Mn ranges from 5000 to 6500 Daltons, and Mw ranges from 12000 to 20000 Daltons.
Because of its high molecular weight, icodextrin is absorbed through the peritoneal membrane more slowly compared to glucose. As a result, the osmotic pressure in case of icodextrin is relatively constant during the dwell, and peritoneal volume slowly increases with greater fluid removal.
Absorbed icodextrin is hydrolyzed by α-amylase by the cleavage of glycosidic bonds to glucose polymers with the degree of polymerization (DP) less than the parent substance. In human serum or plasma, and in the spent dialysate small oligosacharides, including maltose (DP2), maltotriose (DP3), maltotetrase (DP4), maltopentaose (DP5), maltohexaose (DP6), and maltoheptaose (DP7) have been quantified. Eventually, maltose is further metabolized to glucose by malase. After the single 12-hours icodextrin dwell, all metabolites and total icodextrin were characterized up to 28 days post dose.

FORMULATION

Clinical studies with Extraneal 7.5% icodextrin peritoneal dialysis solution used icodextrin manufactured by ML Laboratories. Table 1 describes its molecular weight and branching characteristics.
Table 1. Icodextrin molecular weight and branching characteristics.

Parameters	Specification
Molecular Weight Distribution:	
Weight Average Molecular Weight (Mw) Range	12,000 – 20,000 Daltons
Numerical Molecular Weight Average (Mn) Range	5,000 – 6,500 Daltons
Branching:	
α (1-4)	≥ 90%
α (1-6)	≤ 10%
% Mass Range (Daltons)	
Less than 1,638	< 6%
1,638 – 5,000	12 – 26%
5,000 – 20,000	45 – 66%
20,000 – 45,000	12 – 23%
1,638 – 45,000	> 85%

The peritoneal dialysis solution formulated by the sponsor contained the same composition of electrolytes and lactate as Dianeal PD-2 (NDA 17,512). Table 2 lists the other characteristics of Extraneal used in clinical studies.

Table 2. **Extraneal formulation used in clinical trials**

Component	**Quantity per 100 ml of Solution**
Icodextrin	7.5g
Sodium Chloride	5.35g
Sodium Lactate	4.48g
Calcium Chloride Dihydrate	0.257g
Magnesium Chloride Hexahydrate	0.0508g
Water for injection	qs
Electrolyte	**Concentration (mEq/L)**
Sodium	132
Calcium	3.5
Magnesium	0.5
Chloride	96
Lactate	40
Calculated Osmolality	
pH (Sterilized solution)	5.2

The applicant performed additional formulation feasibility studies, which demonstrated that icodextrin in a broad molecular weight range is suitable as an osmotic agent in peritoneal dialysis. Table 3 lists the formulation's compositions and Table 4 lists the polymer formulations used in these preliminary studies.

Table 3. Drug formulation development.

Study	**Lot No.**	**Dosage Form and Strength**	**Batch Size (bags)**	**Formulation or significant manufacturing change (if any) and reason for change**
Single-Dose Pharmacokinetic Study				
RD-99-CA-060	000A19G42	PDS, Extraneal (7.5% Icodextrin)	[redacted]	Extraneal Formulation No change
Phase III Multi-Dose Studies				
RD-97-CA-130	C378414 C380105 C380972 C380964 W8D06T1 W8D07T1	PDS Extraneal (7.5% Icodextrin)	[redacted]	Extraneal Formulation No change
RD-97-CA-131	C378414 C380105 C380972 C380964 C414813 C414821 C425678 C425660 W8D06T1 W8D07T1 W8D07B3KX W8D06B2	PDS Extraneal (7.5% Icodextrin)	[redacted]	Extraneal Formulation No change
PRO-RENAL-REG-035	96K23G30	PDS 7.5% Icodextrin	[redacted]	Extraneal Formulation No change

Table 4. Glucose polymer formulations for formulation feasibility studies

Study	Formulation		MWD (Daltons) Mw	Mn	Solution Characteristics Osmolality (mOsm/kg)	pH	Sodium (mmol/L)	Calcium (mmol/L)	Lactate (mmol/L)	Cl	Mg	Glucose (mmol/L)	Glucose Polymer (mmol/L)	Solution Manufacturer
MTR(F) MTR(1)	GP1	5%	7,000	960	321	6.1	138	1.9	45			4.0	61	[redacted]
		10%			376	6.0	131	1.9	45			7.7	105	
		15%			412									
MTR(2) MTR(3) MTR(4)	GP2		16,823	5,304	302	5.6	145	1.9	45			0.2	10.3	[redacted]
MTR(5)	GP3	5%	22,000	7,000	272		132	1.75	40*	96	0.25		7.1	[redacted]
		7.5%			277		132	1.75	40	96	0.25		10.7	
		10%			284		132	1.75	40	96	0.25		14.3	
MTR(6)	GP3/G (7.5% GP3 + 0.35% glucose)		20,000	3,000	299		132	1.75	40*	96	0.25	19.5	10.7	[redacted]
MTR(7)	GP3/G (7.5% GP3 + 0.35% glucose)		20,000	3,000	299		125	1.77	40*	96		19.5	12.3	[redacted]

Mn –Numerical Average Molecular Weight; Mw- Weight Average Molecular weight
*Value per C of A from manufacturer

These early studies demonstrated that glucose polymer with Mn of 5304 or above and Mw of 16283 and above has the most favorable ultrafiltration (measurement of PD efficacy) to carbohydrate absorption ratio when formulated in a PD solution at a 5-10% concentration.

ANALYTICAL

Are the analytical method used in this NDA sensitive and accurate?

Were the metabolites measured properly?

Three different analytical methods were applied for the assay of different species. Total icodextrin was assayed in plasma, spent dialysate and urine by [redacted] . This method determines the total mass of all icodextrin polymers with a degree of polymerization of two or larger. This method uses amyloglucosidase to completely hydrolyze the polymers to glucose. Glucose is analyzed before and after hydrolysis and by substraction, the icodextrin concentration is calculated.
Icodextrin metabolites (DP2-DP7) were detected in blood, spent dialysate, and urine by [redacted] and in plasma and urine by [redacted]
The sponsor provided the summary of the methods in Table 5.

The sponsor claimed that [redacted] assay was specific for total icodextrin. However, the assay measurements refer to the bulk sum of glucose polymers and not to the single substance. Therefore, the [redacted] method is lacking specificity.

Table 5. Analytical methodology summary

Study ID	Submission Date	Type of Biological Fluid	Method	Sensitivity of Method Range (mg/L)	Specificity
RD-99-CA-060		plasma; dialysate; urine		LOQ:	Yes for total icodextrin
				LOQ:	Yes for metabolites DP2-DP7
RD-97-CA-130		plasma		LOQ:	Yes for total icodextrin
				LOQ:	Yes for metabolites DP2-DP7
RD-97-CA-131		plasma		LOQ:	Yes for total icodextrin
				LOQ:	Yes for metabolites DP2-DP7
PRO-RENAL-REG-035		Plasma; dialysate		LOQ:	Yes for total icodextrin
				LOQ:	Yes for metabolites DP2-DP7
ML/IB/001 (MIDAS)		Serum		Not available from the report	Yes for DP2, DP3, DP4.
ML/IB/004 (MIDAS2)				Not available from the report	Yes for DP2, DP3, DP4.
ML/IB/014 (S-5)		Serum; dialysate		Not available from the report	Yes for DP2, DP3, DP4.
ML/IB/020 (DIANA)		Serum		Not available from the report	Yes for DP2, DP3, DP4.
ML/IB/011 (DELIA)		Serum; dialysate		Not available from the report	Yes for DP2, DP3, DP4.

In the Table 5 the sponsor indicates the limit of quantitation (LOQ) for [redacted] and [redacted] mg/L. In the analytical method validation report the LOQ is reported as [redacted] mg/L for each of the analyte. All methods were properly validated for accuracy and precision. The [redacted] was validated only for 3 metabolites of icodextrin, and the limit of detection was not reported. It was used in the MIDAS, DIANA, and DELIA studies. Therefore, the incomplete characterization of all molecular entities led to the difficulties in the interpretation of the results of these studies.

Is there interference from laboratory measurements?

Measured serum amylase activity levels in patients with end stage renal disease who use peritoneal diasysis decrease approximately 80 to 90% when using a dialysis solution containing icodextrin. Clinical assay kits for amylase rely on the colorimetric reactions with substrate. The sponsor studied the parameters of the enzyme kinetic for the interpretation of the results for the clinical assay kits. Figure 2 shows the amylase enzyme reaction using 0.71 nM synthetic substrate with zero (diamonds), 0.21, (squares), 0.71 (triangles) and 3.6 (circles) mg/mL icodextrin.

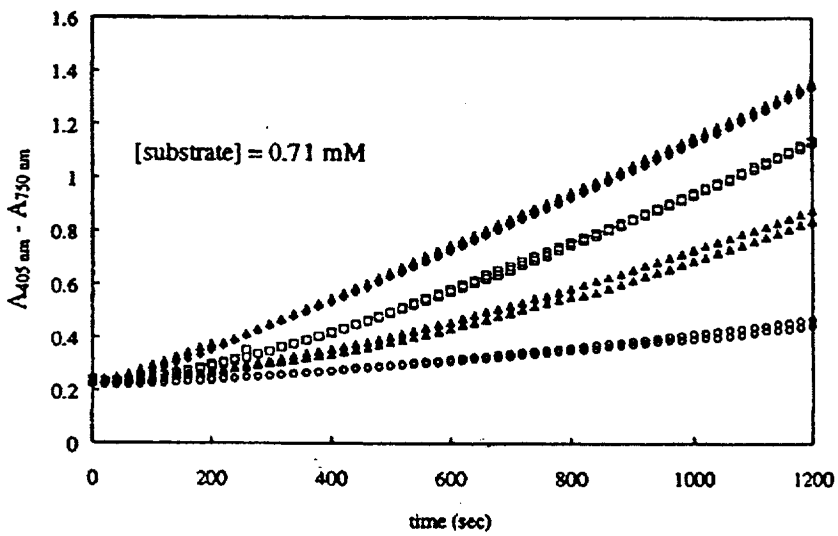


Figure 2. Amylase activity in the presence and absence of icodextrin

Serum amylase activity is competitively inhibited by icodextrin, which acts as an alternative substrate for the enzyme. The level of substrate in the clinical assays varies, therefore, the level of icodextrin required to cause the inhibition will vary. The following factors: assay kit source, test technique, equipment, and sample preparation determine the effect of icodextrin on the measurement of serum amylase. Therefore, the results of this assay should be interpreted carefully.

When icodextrin is used as a PD solution, the laboratory measurements of glucose may overestimate real glucose concentration. The sponsor evaluated twelve enzymatic methods in order to determine potential interference due to icodextrin and its metabolites in blood glucose measurements. Among these assays only Accutrend gives an overestimmation of the glucose value due to the presence of icodextrin. All other methods do not show any interference.

Is icodextrin compatible with other intraperitoneally administered drugs?

In case it is necesssary to treat peritonitis, simultaneously with the administration of the PD solution a variety of antibiotics are coadministered intraperitoneally. Other additives used with the PD solution are insulin for diabetics and heparin to prevent clotting at the catheter. Possible interaction of icodextrin with these drugs either alone or in combination with each other was studied in vitro and in vivo. In vitro incubation of icodextrin up to 36 or 48 hours, does not change the minimum inhibitory concentration (MIC) of gentamicin vancomycin, cefazolin, ceftazidine (Studies, RD-96-PD-041, RD-98-PD-038, RD-96-PD-067, RD-96-PD-135, Table 6 and 7).

Table 6. Activity of the antibiotics after 6 hours incubation with icodextrin

Antibiotic	Organism Tested	Concentration (mg/L)	Time of Analysis (hours)	MIC* (mg/L)
Vancomycin	*B. subtilis*	1000	0, 6	0.49 and 0.98
Cefazolin	*S. aureus*	500	0, 6	0.98 and 0.98
Magnapen	*M. luteus*	2000	6	**
Magnapen	*S. aureus*	2000	6	0.24
Ceftazidime	*S. aureus*	500	0, 6	7.81 and 7.81
Gentamicin	*B. pumilis*	70	0, 6	0.14 and 0.14
Ampicillin	*M. luteus*	1000	0, 6	≤0.06 and ≤0.06
Amphotericin	*S. cerevisiae*	4	0, 6	1.0 and 1.0

*MIC: Lowest concentration of the drug that will inhibit bacterial culture growth.
**This organism was resistant to the antibiotic under test conditions.
Source: Report 91/3546/MB

APPEARS THIS WAY
ON ORIGINAL

Table 7. Drug compatibility with the other drugs.

	Heparin	Gentamicin	Vancomycin	Insulin I	Insulin II	Cefazolin	Ceftazidime	Netilmycin
Other drugs present	Vancomycin + insulin	Vancomycin + insulin	Heparin + insulin	None	Heparin, gentamicin, vancomycin	None	None	None
Low Conc. High Conc.	1250 U/L 2270 U/L	4 mg/L 68 mg/L	20 mg/L 909 mg/L	2 U/L 57 U/L	2 U/L 57 U/L	250 mg/L 750 mg/L	125 mg/L 500 mg/L	4 mg/L 60 mg/L
Method								
Temperature (°C)	25, 27	25, 37	25, 37	25, 37	25, 37	25, 37	25, 37	25, 37
Time of Analysis	0, 24, 26, 28, 48 hrs	0, 24, 26, 28, 48 hrs	0, 24, 26, 28, 48 hrs	0, 24, 28, 48 hrs	0, 24, 26, 28, 48 hrs	0, 24, 26, 28, 36 hrs	0, 24, 26, 28, 36 hrs	0, 24, 26, 28, 36, 48 hrs
Visual inspection	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
pH	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable
Particulate matter (48 hours)	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
% original activity								
24 hrs (Low: High)	99%: 99%*	101%: 102%	98%: 99%	82%: 86%	88%: 104%	97%: 94%	97%: 96%	105.4%: 100.9%
26 hrs	99%: 99%	104%:102%	98%: 99%	-----	95%: 98%	97%: 95%	97%: 97%	102.4%: 99.4%
28 hrs	100%: 98%	101%:101%	96%: 99%	87%: 87%	93%: 91%	97%: 94%	96%: 95%	104.8%: 99.1%
36 Hrs	----	-----	----	-----	----	94%: 91%	90%: 89%	98.6%: 105.2%
48 hrs	98%: 103%	101%:101%	96%: 99%	84%: 80%	91%: 76%	93%: 93%	92%: 90%	113.3%: 106.7%
Report	RD-96-PD-041	RD-96-PD-041	RD-96-PD-041	RD-96-PD-067	RD-96-PD-067	RD-98-PD-038	RD-98-PD-038	RD-96-PD-135

t=26 hrs: 24 hrs at 25°C + 2 hrs at 37°C.
t = 28 hrs: 24 hrs at 25°C + 4 hrs at 37°C
*The two % activities represent % original activity for low and high doses of drugs.

Insulin in lost more than 10% of its potency (in vitro study, Table 7).

Table 7. Insulin feasibility study

[illegible]	t = 0 25 °C (u/L)	t = 24 hrs 25 °C (u/L)	% chg	t = 28 hrs (u/L)	% chg	[illegible] % recovery @ t = 0
AI-1	1.80	1.35	-25.00	1.60	-11.11	
AI-2	1.75	1.55	-11.43	1.50	-14.29	
AI-3	1.90	1.55	-18.42	1.65	-13.16	
average	1.82	1.48	-18.28	1.58	-12.85	90.83
CI-1	1.50	0.95	-36.67	1.05	-30.00	
CI-2	1.35	1.00	-25.93	1.00	-25.93	
CI-3	1.35	0.95	-29.63	1.10	-18.52	
average	1.40	0.97	-30.74	1.05	-24.81	79.55
BI-1	49.10	47.15	-3.97	52.20	6.31	
BI-2	65.45	52.65	-19.56	48.85	-25.36	
BI-3	61.05	49.10	-19.57	48.95	-19.82	
average	58.53	49.63	-14.37	50.00	-12.96	102.69
DI-1	46.30	32.15	-30.56	35.25	-23.87	
DI-2	45.25	34.30	-24.20	35.65	-21.22	
DI-3	42.75	35.30	-17.43	38.55	-9.82	
average	44.77	33.92	-24.06	36.48	-18.30	89.53

AI 1to 3 = polyglucose solution with 2 u/L insulin
CI 1 to 3 = Dianeal with 1.76 u/L insulin
BI 1 to 3 = polyglucose solution with 57 u/L insulin
DI 1 to 3 = Dianeal with 50 u/L insulin

t = 28 hrs: 24 hrs at 25 °C + 4 hrs at 37 °C
% chg: percent change from t = 0

Heparin was fully compatible.

Additionally to the in vitro studies, the sponsor performed a pilot study in 6 patients in order to determine if insulin can be administered in combination with icodextrin to CAPD patients with diabetis mellitus. This study ML/IB/002 was designed as an open crossover study to compare the rate of absorption of insulin from peritoneal CAPD fluid containing 7.5% icodextrin or 1.36% glucose as the osmotic agents. The blood samples were taken during the 6 hours of the dwell, bag weights were measured to estimate the ultrafiltration. The differences in insulin levels in both plasma and dialysate fluid were not statistically significant (p= 0.67 and p= 0.22, respectively). Figure shows the plasma and CAPD liquid mean levels of insulin during the dwell.

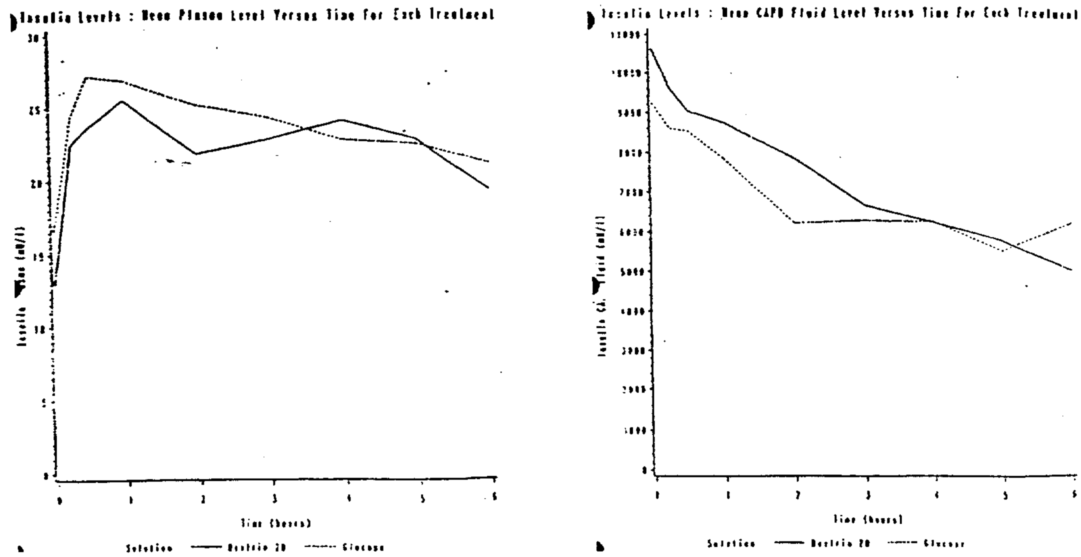


Figure 3. Mean plasma and CAPD fluid concentrations of insulin.

Although the sample size was small, the sponsor concluded that insulin may be safely administered together with icodextrin, the same way that it is added to glucose CAPD fluid. Therefore, insulin was used as an addition to the dialysate in the study ML/IB/001 (MIDAS).

HUMAN PHARMACOKINETICS

Were there bioavailability and/or bioequivalence issues?

Solutions for peritoneal dialysis are administered parenterally into the peritoneal cavity, directly to the side of action. Therefore, PD solutions are considered fully bioavailable immediately upon instillation and the study of bioavailability is not needed. The solute and water removal starts when the diffusive and osmotic pressure gradients are established, right after the administration. The volume of instilled solutions determines the bioavailability of PD solution.

There are no bioequivalence issues since only one formulation has been investigated in clinical studies and is the to-be-marketed formulation of Extraneal.

What are the exposure-related pharmacokinetics properties of the drug?

The applicant evaluated the pharmacokinetics of a single dose 12-hours exchange of 7.5% icodextrin peritoneal dialysis solution in patients treated with peritoneal dialysis (Study RD-99-CA-60). The concentration of total icodextrin, and its metabolites (DP2 to DP7) were quantitated in dialysate, plasma, and urine. Out of 13 enrolled patients 11 have completed the study through day 28. There were 5 males and 8 females; 6 Caucasians, 6 blacks, and one Hispanic patient. The mean age was 53.8 years with the range of 29 to 77 years. Peak total icodextrin (icodextrin and its degradation products) plasma concentrations, median of 2.23 g/L, was achieved at median Tmax of 12.7 hours. Total icodextrin plasma concentrations at steady state was about 5 g/L.

What are the kinetics of icodextrin absorption from the peritoneal cavity?

Peritoneal absorption of icodextrin was evaluated by monitoring the total icodextrin concentrations in the peritoneal cavity. The absorption was described with zero-order kinetics. This is consistent with convective transport by peritoneal lymphatic pathways. The change of total icodextrin concentrations in peritoneal cavity is shown in Figure 4.

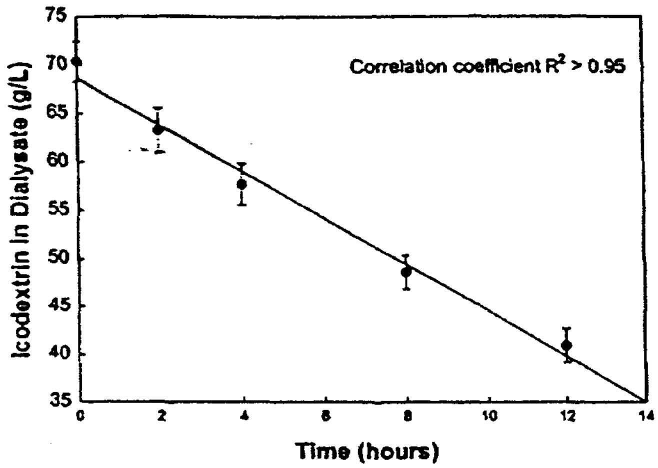


Figure 4. Mean concentration of total icodextrin in peritoneal cavity

The sponsor performed the modeling of the individual patient's data with the SAS program; however, the input and output files were not available for review. The median amount of icodextrin absorbed from the peritoneal cavity into plasma was 60.2 g (40.1%) with range of 36.3-102.4 g, median rate of disappearance was calculated as 5.02 g/hr (range 3.02-8.53 g/hr). The individual patients absorption rates are shown in Table 8.

Table 8. Dose of icodextrin absorbed during 12 hours and zero-order disappearance rate constant.

Patient	Dose=A_t (g)	K_0 (g/hr)	Absorption %
101			
103			
104			
105			
106			
107			
201			
202			
203			
204			
301			
302			
304			
Mean	62.13	5.1776	41.42
Std Err	5.11	0.4258	3.41
Minimum			
Median	60.24	5.0204	40.16
Maximum			

How does the concentrations of the icodextrin metabolites change in the dialysate?

The concentrations of all metabolites were measured in the dialysate during the 12-hour dwell. Again, the highest concentrations of small polymers occur at the beginning of the dwell, and the concentration of the larger polymers increase at the end of the dwell (Figure 5).

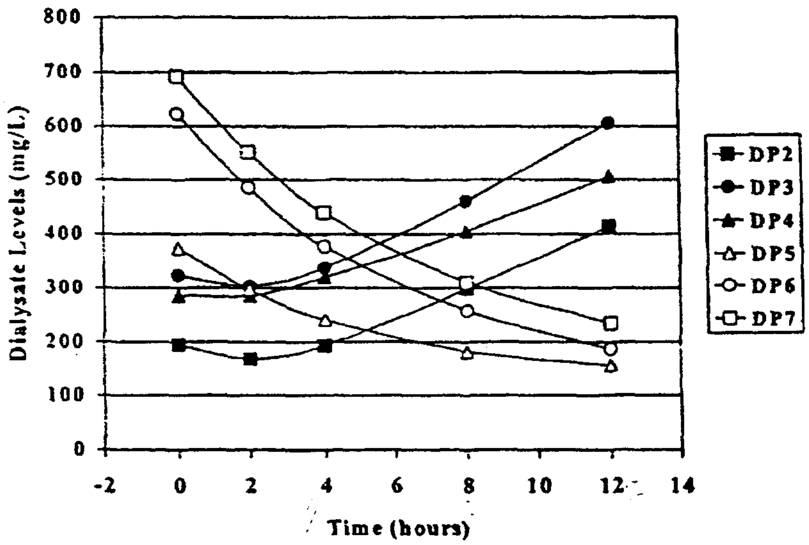


Figure 5. Mean DP2-DP7 dialysate levels vs time. Symbols are the observed data, and curves are the smoothing lines.

This graph indicates a possible formation of the smaller polymers during the dwell either by hydrolysis, or by reabsorption from blood.
After the single 12-hours dwell with icodextrin, the same patients received three exchanges with glucose. Icodextrin and its metabolites were recovered in all three spent dialysates. The total icodextrin and its metabolites concentrations in dialysate are shown in Table 9.

Table 9. Concentration of Icodextrin and Metabolites DP2-DP4 in Dialysate from 3 Exchanges after the Single 12-hour Exchange

Icodextrin or Metabolites	Concentration (g/L)		
	1st exchange	2nd exchange	3rd exchange
DP2	0.27 ± 0.031	0.29 ± 0.039	0.24 ± 0.024
DP3	0.26 ± 0.034	0.25 ± 0.035	0.18 ± 0.021
DP4	0.12 ± 0.017	0.075 ± 0.011	0.039 ± 0.007
Sum of DP2-DP4	0.65	0.62	0.46
Icodextrin	3.41 ± 0.55	0.85 ± 0.11	0.47 ± 0.05

What are the characteristics of icodextrin plasma kinetics?

Total icodextrin was measured in plasma for 28 days after the single 12 hours dwell. After day 7, mean plasma icodextrin concentrations return to the baseline values. It is not clear why there is measurable icodextrin plasma concentrations at baseline (Day 0, time 0, as reported by the sponsor). These values are most likely overestimated the mean value of 63.9 mg/L obtained at time 0 and should be interpreted with caution. Most likely it is a sign of a false positive signal due to the lack of assay specificity.

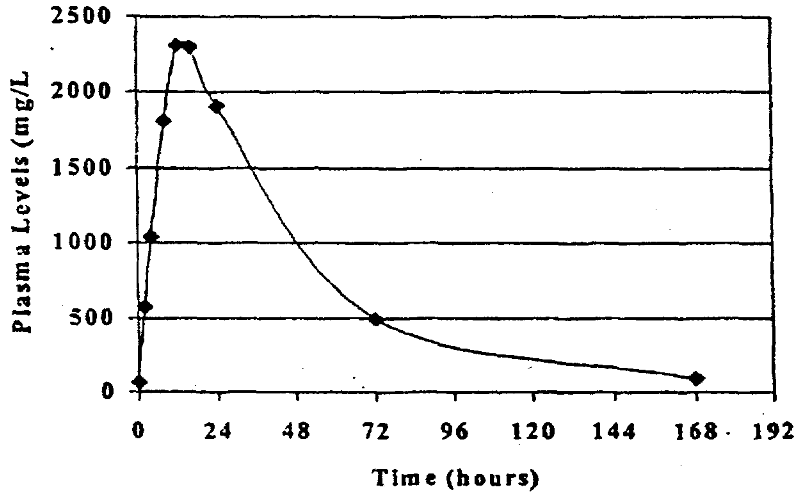


Figure 6. Total Icodextrin plasma concentration vs time

The sponsor's Figure 6 presents the total icodextrin data only up to day 7 post dose. Visual inspection of this plot may suggest the possibility of the use of a one-compartmetal model (1CM). However, visual analysis of the data up to day 28 in **Figure 7** indicates that the decline of total icodextrin plasma concentrations may have a more complex character than a 1CM.

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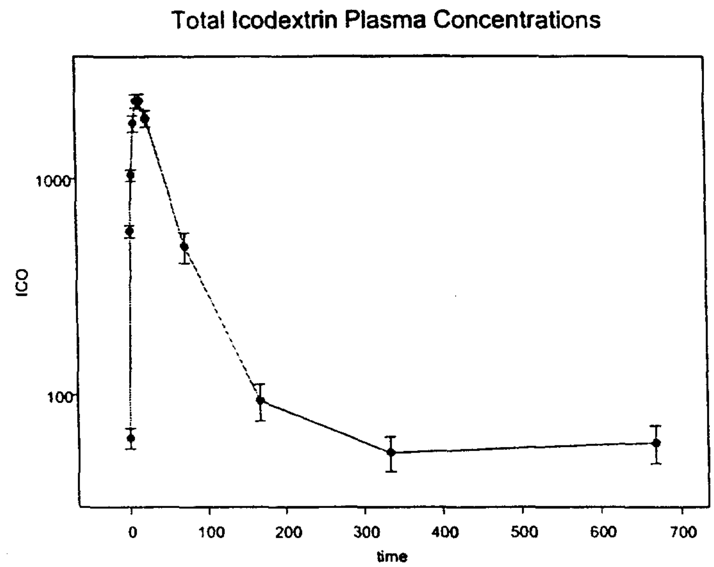

Figure 7. Total Icodextrin plasma concentrations after the single dwell.

Moreover, Figure 7 shows the summation of all glucose polymers in plasma. The sponsor modeled the data for total icodextrin assuming that it is a one molecular entity and described its kinetics with one compartmental model with zero order absorption. The pharmacokinetic parameters estimated by the sponsor are shown in Table 10.

Table 10. Estimates of pharmacokinetic parameters of icodextrin

Patient	K_e (/hr)	Clearance Rate (L/hr)	T_{max} (hrs)	C_{Peak} (mg/L)	Distribution Volume (L)	AUC (g/L/hr)	Half Life (hrs)
101							
103							
104							
105							
106							
107							
201							
202							
203							
204							
301							
302							
304							
Mean	0.0475	1.0946	12.77	2294.91	22.73	125.28	15.20
Std Err	0.0027	0.1413	0.15	164.70	2.31	13.43	0.89
Minimum							
Median	0.0470	1.0893	12.70	2231.38	20.06	153.69	14.73
Maximum							

Although the absorption rate of total icodextrin in plasma has been mentioned in the model used, neither mean nor individual estimated values were reported by the sponsor. The pharmacokinetic parameters for total icodextrin presented by the sponsor are difficult to interpret because they are related to the bulk measurement of all glucose polymers and cannot be considered reliable. For example, the sponsor calculated the half-life of total icodextrin as 14 hours. This value seems to be dramatically underestimated considering that the drug is still circulated in plasma at day 7 and that after the multiple dwells icodextrin plasma concentrations reach steady state at week 2. The sponsor reported the mean volume of distribution as 20 L suggesting the distribution in the intercellular space. The distribution of the glucose polymers of different molecular weight will strongly depend on their molecular weight, and thus the calculated value of the mean volume of distribution is far from reality. The sponsor's calculated parameters should not be included in the Package insert.

Prediction of the steady state plasma levels of icodextrin using the sponsor's proposed model is meaningless.

Were the metabolites of icodextrin properly characterized?

The sponsor performed a comprehensive characterization of all icodextrin metabolites in plasma and dialysate with the degree of glucose polymerization from 2 (DP2) to 7 (DP7). **Figure 8** shows all metabolites characterized in plasma.

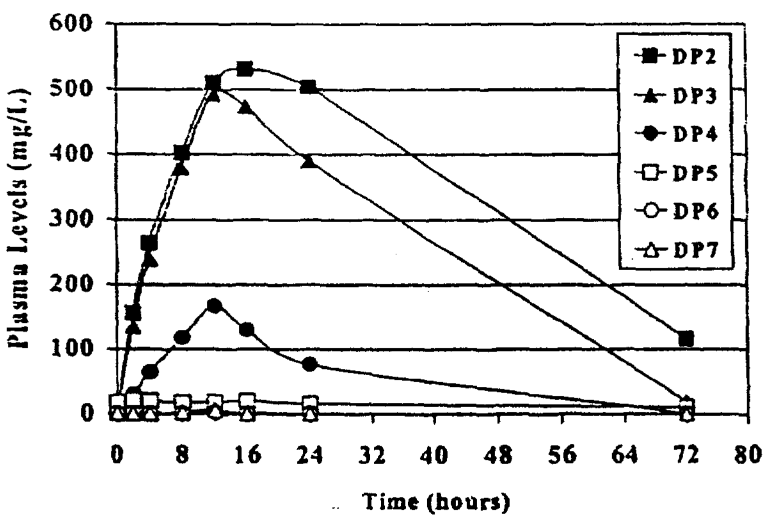

Figure 8. Profiles of the mean plasma concentrations of glucose polymers.

The concentrations of small oligosaccharide metabolites DP2, DP3, and DP4 in plasma were similar to the parent drug. The highest plasma concentrations were measured for maltose, DP2. The level of glucose in plasma did not increase significantly. For all polymers (DP2 to DP7), their plasma concentrations were measurable at the baseline. After that, the level of larger polymers seems to be very low **(Figure 8)**.

However, careful analysis of the submitted data indicates that there were almost no differences in plasma concentrations of the metabolite DP5 at Day 0 and day 28. **Figure 9** shows the profiles of icodextrin metabolites in plasma after the single dwell. Plasma DP6 concentrations increased from 0.90 mg/L to 3 mg/L at 12 hours (end of the dwell), and were measurable up to 28 days. Plasma DP7 concentrations changed from 0.77 (time 0) to 7.38 mg/L (12 hours), and were measurable up to day 7.

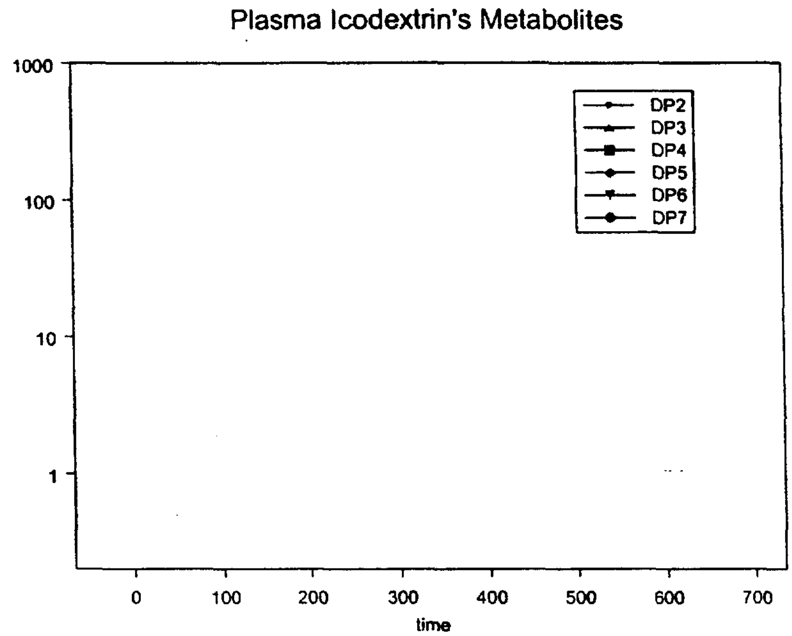

Figure 9. Icodextrin's metabolites plasma concentrations vs time

The **mean values** of icodextrin metabolites in plasma calculated at the end of the 12 hours dwell are shown in **Figure 10**.

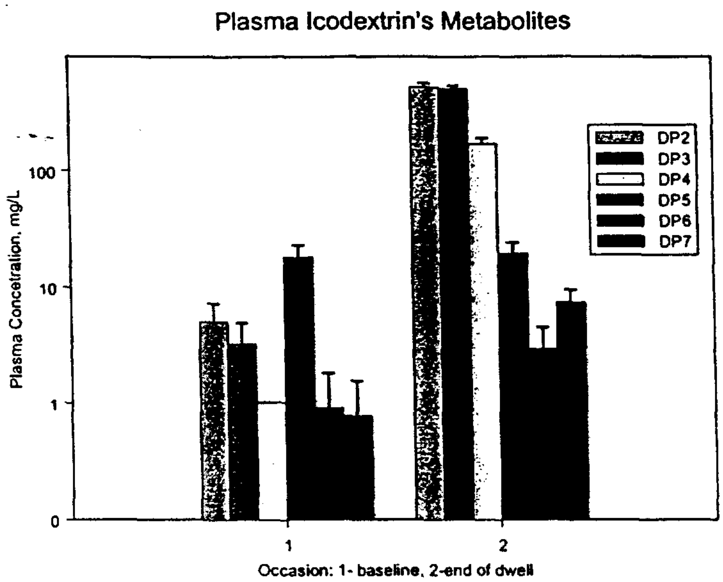

Figure 10. Mean and SD of icodextrin metabolites in plasma. 1 denotes the measurements at baseline, 2, at the end of the 12 hours dwell.

Figure clearly shows that the plasma concentrations of larger polymers (DP5-DP7) are very similar at the baseline and at the end of dwell.
The applicant did not perform any pharmacokinetic modeling for any of the metabolites of icodextrin.

How is icodextrin excreted?

Urinary excretion of Icodextrin was examined during the first 24 hours of the study. Four patients were anuric. The mean creatinine clearance for the other 9 patients was 5.0 ± 1.5 mL/min, while urea clearance was 1.8 ± 0.73 mL/min. In the 24-hour urine collection, a mean of 2.2 ± 0.6 g of icodextrin was recovered. The icodextrin urinary excretion directly correlates with creatinine clearance. The R value obtained by the Agency was slightly lower (0.79) than the one reported by the sponsor (0.82), see Table 11 and Figure 11.

Table 11. Regression statistics for the urinary excretion and creatinine clearance values of icodextrin

Regression Statistics		
Multiple R	0.797454482	
R Square	0.63593365	0.797454482
Adjusted R Square	0.51093365	
Standard Error	1124.644213	
Observations	9	

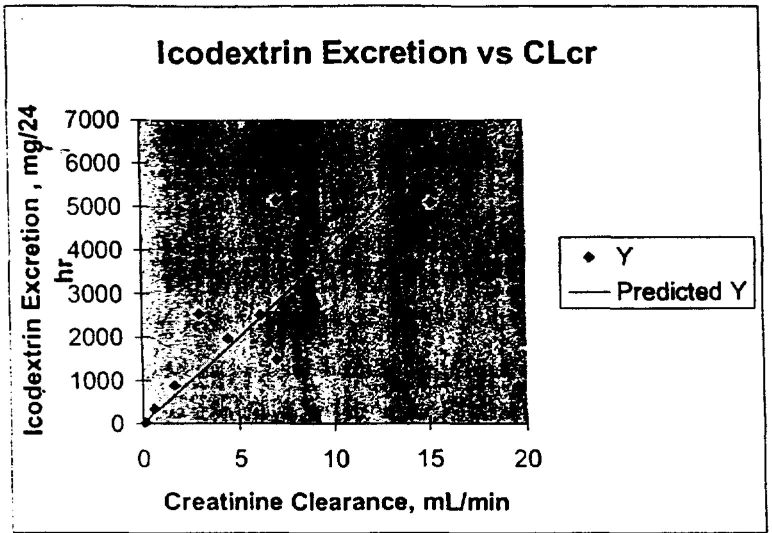

Figure 11. Correlation of icodextrin excretion and creatinine clearance

The average daily excretion was 473 ± 77 mg/mL of creatinine clearance.

How was the clinical effect of peritoneal dialysis measured?
Was it correlated to the dose and/or concentration of the drug (Pharmacodynamics)?

A classical PK/PD study for Extraneal was not performed. The effect of the PD solution is measured by its ultrafiltration. Icodextrin is administered as 7.5% solution. The relationship between icodextrin and/or its metabolites concentrations in plasma, urine or spent dialysate were not established. However, clinical studies of chronic administration of Icodextrin showed a superior ultrafiltration compared to the exchange with 2.5% dextrose.
An adequate exposure-response or dose-response relationship could not be established due to the fact that the sponsor did not conduct dose ranging studies of icodextrin and that in all the studies the same concentration of icodextrin solution was used.

What was the exposure of icodextrin and its metabolites at the steady state?

Icodextrin and its metabolite concentrations were measured in plasma at steady state in several multiple doses studies; however, due to the problems with the assay, only results of three of them: RD-97-CA-130, RD-97-CA-131, and PRO-RENAL-REG-035 are interpretable. Steady state total icodextrin (icodextrin and its degradation products) plasma concentrations ranged from 4 to 6.5 g/L and were consistent between studies (**Figure** 12). Steady state levels were achieved in about one week and remained consistent throughout the duration of exposure to icodextrin.

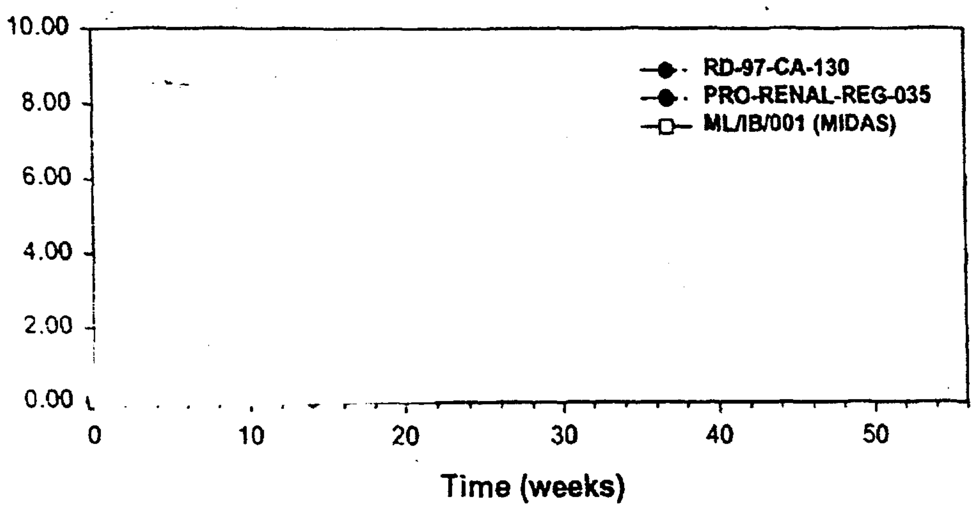

Figure 12. Icodextrin plasma levels in multiple dose studies.

Metabolites DP2-DP4 **plasma** concentrations are shown in Figure 13. Steady state levels of DP5-DP7 were similar to the baseline values (as was shown in a single dose study) and were not shown in **Figure 13.** Steady state maltose levels ranged from 0.81 to 1.35 g/L. Levels of DP3 were similar, and the levels of DP4 were significantly lower.
No accumulation of icodextrin and its metabolites was observed in the chronic dose studies up to 52 weeks.

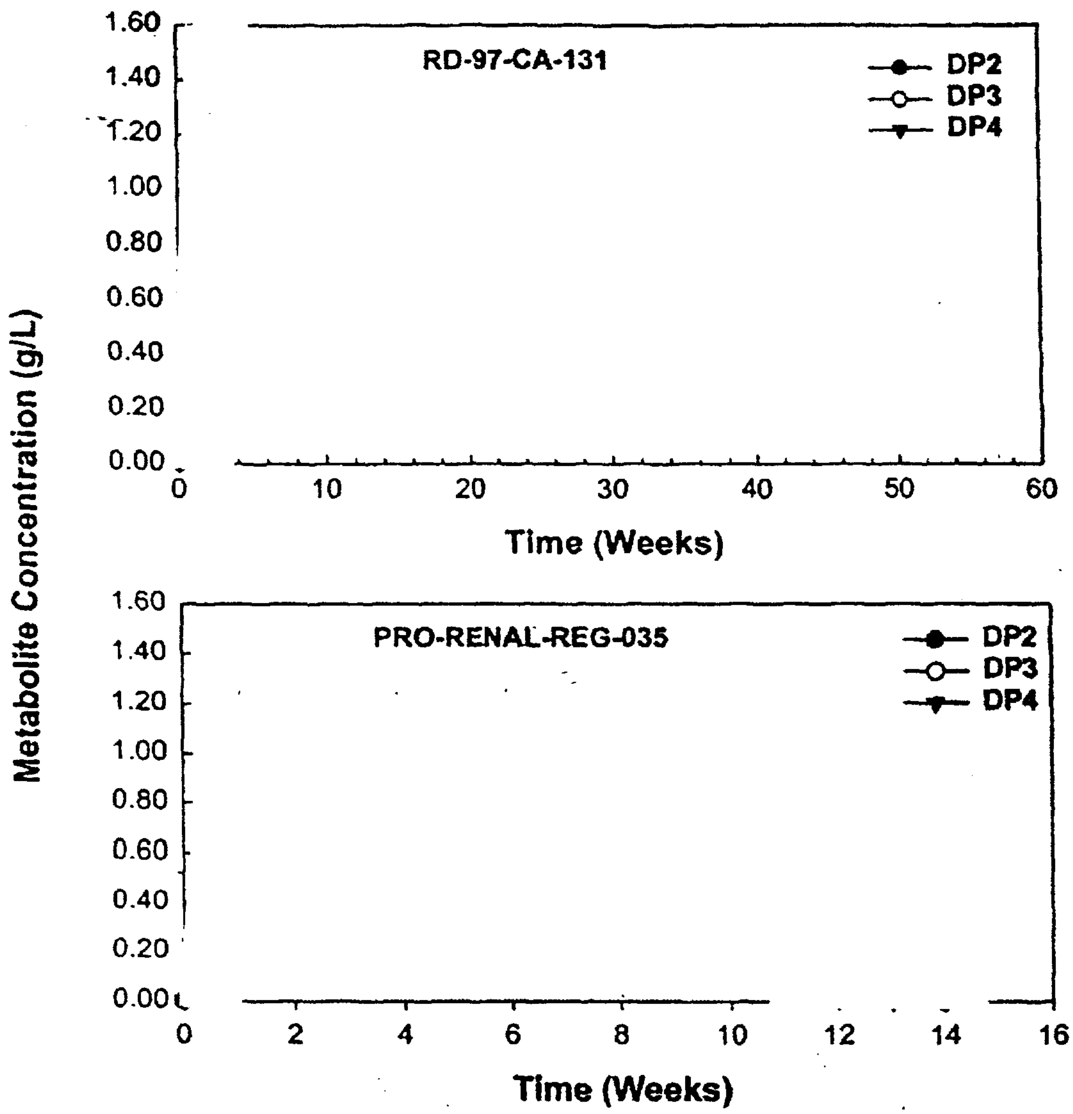

Figure 13. Low molecular weight glucose polymers in plasma at steady state dosing up to 12 weeks (Study PRO-RENAL-REG-035) and up to 52 weeks RD-97-CA-131.

How efficient was the elimination of icodextrin after the multiple doses?

Since icodextrin was found in patient's plasma up to 28 days after the single 12-hour dwell, its elimination after the multiple doses was studied. In the study PRO-RENAL-REG-035, patients were randomized to receive dextrose or Extraneal for 12 weeks. After that, they were to receive dextrose. Plasma icodextrin concentrations were measured prior to use of icodextrin, at week 1, 6, and 12 of icodextrin use and at weeks 13 and 14. At the week 14 the levels of icodextrin came back to the **baseline measurements (Figure 14)**.

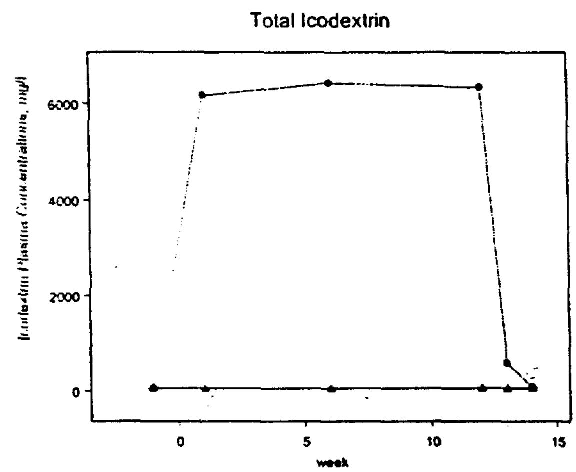

Figure 14. Total icodextrin plasma concentrations vs time

In conclusion, multiple Phase 3 studies showed that about 30-40% of icodextrin was absorbed from the peritoneal cavity. Plasma levels of icodextrin and its metabolites reach steady state within a week. Icodextrin concentrations at steady state are about 4.5 to 6.0 g/L. After one year of chronic dosing of Extraneal no accumulation was observed for either the parent drug or for metabolites. After the termination of icodextrin, levels of the drug and its metabolites return to baseline within approximately 2 weeks regardless of the duration of exposure. The summary pharmacokinetic results are shown in Table 12.

Table 12. Summary of the pharmacokinetic results.

Single-Dose Pharmacokinetics

Study	Route of Administration/Dosage Form/Dose	T_{max}	Vd	AUC	$T_{1/2}$	Urinary Excretion	CLp or C_{max}	CLr	Net Abs.%	Plasma level (g/L) of Icodextrin	Maltose
RD-99-CA-060	IP/PDS – Extraneal (7.5% Icodextrin) Single (12 hour dwell) exchange.	12.70 hrs (median)	20.06 L (median)	153.69 g/L/hr (median)	14.73 Hrs (median)	2.22 g/24hrs (mean)	2231.38 mg/L (median)	1.09 L/hr (median)	40.16 % (median)	5.26 g/L (predicted steady-state level)	

Phase III Multi-Dose Studies

Study	Route of Administration/Dosage Form/Dose	T_{max}	Vd	AUC	$T_{1/2}$	Urinary Excretion	CLp or C_{max}	CLr	Net Absorption (%)	Plasma level (g/L) of Icodextrin	Maltose
RD-97-CA-130	IP/PDS - Extraneal (7.5% Icodextrin) Daily long dwell exchange up to 4 weeks								not determined	Wk 4: 5.08 ± 0.21	0.85± 0.03
RD-97-CA-131	IP/PDS - Extraneal (7.5% Icodextrin) Daily long dwell exchange up to 52 weeks								not determined	Wk 4: 5.03 ± 0.21 Wk 13: 5.02 ± 0.16 Wk 26: 4.76 ± 0.17 Wk 39: 5.07 ± 0.19 Wk 52: 5.00 ± 0.21	0.84 ± 0.03 0.85 ± 0.03 0.81± 0.03 0.85± 0.03 0.82 ± 0.03
PRO-RENAL-REG-035	IP/PDS – Extraneal (7.5% Icodextrin) Daily long daytime dwell up to 12 weeks (APD)								Wk 1: 12.5%, Wk 6: 31.7% Wk 12: 32.6% @12hrs	Wk 1: 6.19 ± 0.40 Wk 6: 6.43 ± 0.48 Wk 12: 6.34 ± 0.48 Wk 13: 0.60 ± 0.15 Wk 14: 0.083 ± 0.014	1.11 ± 0.06 1.11 ± 0.07 1.06 ± 0.08 0.088 ± 0.025 0.001 ± 0.001
ML/IB/001 (MIDAS)	IP/PDS – Extraneal (7.5% Icodextrin) Single, daily (8-12 hour) exchange for 6 months.								not determined	Wk 5: 4.87 ± 1.55 Wk 13: 4.41 ± 1.36 Wk 25: 4.62 ± 1.46	1.20 ± 0.38 1.01 ± 0.35 1.09 ± 0.36
ML/IB/004 (MIDAS 2)	IP/PDS – Extraneal (7.5% Icodextrin) Single, daily exchange for up to 42 months.								Not determined	Mo 3: ~4.5 Mo 6: ~5.0 Mo 12: ~4.8 Mo 18: ~4.9 Mo 24: ~4.8	~1.0 ~1.1 ~1.2 ~1.2 ~1.2

Table 12, cont.

Phase III Multi-Dose Studies (continued)

Study	Route of Administration/Dosage Form/Dose	T_{max}	Vd	AUC	$T_{1/2}$	Urinary Excretion	CLp or C_{peak}	CLr	Net Absorption (%)	Plasma level (g/L) of Icodextrin	Plasma level (g/L) of Maltose
ML/IB/014 (S-5)	IP/PDS – Extraneal (7.5% Icodextrin) Open label extension of ML/IB/001 (MIDAS). 24 months of single exchange of 7.5% Icodextrin (MIDAS Study), 3-week washout, 3 weeks of single daily exchange of 7.5% icodextrin in patients with ESRD. Elimination and absorption of icodextrin & metabolites – following cessation and restarting of therapy- in plasma.								40.0 ± 11.9% @~9hrs	Day 1: 4.84 ± 0.82 Day 3: 2.32 ± 0.58 Day 5: 1.08 ± 0.41 Day 8: 0.53 ± 0.21 Day 11: 0.39 ± 0.13 Day 15: 0.37 ± 0.12 Day 22: 0.35 ± 0.11 Day 26: 4.18 ± 0.74 Day 29: 4.63 ± 0.91 Day 33: 4.74 ± 1.26 Day 36: 4.73 ± 0.97	1.15 ± 0.18 0.61 ± 0.14 0.26 ± 0.11 0.08 ± 0.05 0.06 ± 0.02 0.05 ± 0.02 0.04 ± 0.02 1.03 ± 0.19 1.14 ± 0.20 1.21 ± 0.32 1.17 ± 0.16
ML/IB/020 (DELIA)	IP/PDS – Extraneal (7.5% Icodextrin) Daily long daytime dwell of 14-16 hrs in APD patients for 6 weeks. The study consisted of a two-week run-in period, six weeks on the first treatment, four-week washout period, six weeks on the second treatment, and two weeks post study period.								46 ±7% @16hrs	Wk 3: 4.39 ± 1.94 Wk 6: 4.4 ± 0.95	1.0 ± 0.44 1.15 ± 0.31
ML/IB/011 (DIANA)	IP/PDS – Extraneal (7.5% Icodextrin) Daily long daytime dwell of 12-16 hrs in APD patients up to 24 months.								Not determined	Mo 3: 5.53 Mo: 6: 5.22 Mo 9: 5.26 Mo 12: 4.51 Mo 15: 5.43 Mo 18: 4.28 Mo 21: 5.86 Mo 24: 5.71	1.2 1.16 1.14 1.1 1.35 0.94 1.31 1.15

Table 12, cont.

Phase III Multi-Dose Studies (continued)											
Study	**Route of Administration/Dosage Form/Dose**	T_{max}	Vd	AUC	$T_{1/2}$	**Urinary Excretion**	CLp or C_{peak}	CLr	**Net Absorption (%)**	**Plasma level (g/L) of Icodextrin**	**Maltose**
ML/IB/014 (S-5)	IP/PDS – Extraneal (7.5% Icodextrin) Open label extension of ML/IB/001 (MIDAS). 24 months of single exchange of 7.5% Icodextrin (MIDAS Study), 3-week washout, 3 weeks of single daily exchange of 7.5% icodextrin in patients with ESRD. Elimination and absorption of icodextrin & metabolites – following cessation and restarting of therapy- in plasma.								40.0 ± 11.9% @~9hrs	Day 1: 4.84 ± 0.82 Day 3: 2.32 ± 0.58 Day 5: 1.08 ± 0.41 Day 8: 0.53 ± 0.21 Day 11: 0.39 ± 0.13 Day 15: 0.37 ± 0.12 Day 22: 0.35 ± 0.11 Day 26: 4.18 ± 0.74 Day 29: 4.63 ± 0.91 Day 33: 4.74 ± 1.26 Day 36: 4.73 ± 0.97	1.15 ± 0.18 0.61 ± 0.14 0.26 ± 0.11 0.08 ± 0.05 0.06 ± 0.02 0.05 ± 0.02 0.04 ± 0.02 1.03 ± 0.19 1.14 ± 0.20 1.21 ± 0.32 1.17 ± 0.16
ML/IB/020 (DELIA)	IP/PDS – Extraneal (7.5% Icodextrin) Daily long daytime dwell of 14-16 hrs in APD patients for 6 weeks. The study consisted of a two-week run-in period, six weeks on the first treatment, four-week washout period, six weeks on the second treatment, and two weeks post study period.								46 ±7% @16hrs	Wk 3: 4.39 ± 1.94 Wk 6: 4.4 ± 0.95	1.0 ± 0.44 1.15 ± 0.31
ML/IB/011 (DIANA)	IP/PDS – Extraneal (7.5% Icodextrin) Daily long daytime dwell of 12-16 hrs in APD patients up to 24 months.								Not determined	Mo 3: 5.53 Mo: 6: 5.22 Mo 9: 5.26 Mo 12: 4.51 Mo 15: 5.43 Mo 18: 4.28 Mo 21: 5.86 Mo 24: 5.71	1.2 1.16 1.14 1.1 1.35 0.94 1.31 1.15

Table 12, cont.

Study	Route of Administration/Dosage Form/Dose	T_{max}	V_d	AUC	T1/2	Urinary Excretion	CLp or C_{peak}	CLr	Net Absorption (%)	Plasma level (g/L) of Icodextrin	Maltose
Phase II Feasibility and Formulation Studies											
MTR(1)	IP/PDS – 5% GP1, 10% GP1 Single exchange with a 6-hour dwell.					4.8% 2.5% of absorbed polymer for 5% an 10% of GP			5% GP1: 54.8 ± 6.1% 10% GP1: 53.4 ± 7.5% @ 6 hrs	2.64± 0.33 5.32± 0.74	1.0 - 1.5 1.5 - 2.0
MTR(2)	IP/PDS – 5% GP2 Two separate and a week apart single exchanges with 6-hour dwell.								35.6 ± 7.8% @6 hrs	not determined	not determined
MTR(3)	IP/PDS – 5% GP2 Single exchange with a 6-hour dwell.					0.83 ± 0.53 g/L.			14.4 ± 2.6% @6 hrs	1.09 ± 0.17	~ 0.2
MTR(4)	IP/PDS - 5% GP2 Three consecutive exchanges of 6, 8, and 12-hours duration.								22.8 ± 4.12% @6 hrs 24.0 ± 1.65%@8 hrs 26.9±2.89%@12hrs	~ 3.8 after 3 consecutive exchanges	~0.3 1st dwell ~0.5 2nd dwell ~0.9 3rd dwell
MTR(5)	IP/PDS–5%, 7.5%, 10% GP3-hyposmolar Single exchange for a 12-hour dwell								5% GP3: 27.4 ± 4.7% 7.5% GP3: 24.3 ± 2.2% 10% GP3: 21.5 ± 2.0% @12 hrs	0.904 1.63 1.84	0.268 0.288 0.244
MTR(6)	IP/PDS- 7.5% GP3 + 0.35% glucose Single exchange for a 12-hour dwell								32.0 ± 4.0% @12hrs	No significant difference from previous studies	
MTR(7)	IP/PDS – 7.5% GP3 + 0.35% glucose. Daily exchange for a 12-hour overnight dwell for 10 days.					9-29% of the absorbed GP load			31.3 ± 0.8 @12hrs	4.5 (returned to baseline value within 5 days after discontinuation of GP)	0.85

Was the pharmacokinetics of icodextrin studied in special populations?

In the Phase 2 studies, the demographic distribution of female and male patients, as well as the patients of white, black and other races was balanced. Statistical analysis of the data from ~~the~~ study RD-97-CA-130 examined the effects of gender, study site, race, and diabetes on the treatment. Effects of race, diabetes, and site on the net ultrafiltration were marginal. Age category and gender effects were not significant. The influence of diabetes on urea nitrogen clearance and age on creatinine clearance were marginally significant ($p \leq 0.10$). Statistical model input and output files were not available for review.
The applicant did not attempt to evaluate statistically the influence of demographics as well as disease state, and diabetic status on the pharmacokinetics of icodextrin and/or its metabolites.

LABELING RECOMMENDATIONS

1. In the section CLINICAL PHARMACOLOGY instead of the paragraph

Should be:

2. In the section CLINICAL PHARMACOLOGY instead of the paragraph

Should be:

3. In the section on SPECIAL POPULATION instead of the paragraph

Should be:
The influence of age on the pharmacokinetics of icodextrin and its metabolites was not assessed.

4. In the section on SPECIAL POPULATION instead of the paragraph

[redacted]

Should be:
The influence of gender and race on the pharmacokinetics of icodextrin and its metabolites was not assessed.

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APPENDIX I
PROPOSED PACKAGE INSERT

15 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX II
REVIEW OF INDIVIDUAL STUDIES

STUDY RD-99-CA-060

A Study to Evaluate the Pharmacokinetics of a Single Exchange of 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Peritoneal Dialysis

Study ID: RD-99-CA-060 Volume: 1.14-15

Investigators and study centers:	

Objectives:	The purpose of this study was to evaluate the pharmacokinetics of a single 12-hour exchange of 7.5% icodextrin peritoneal dialysis solution in patients treated with peritoneal dialysis.

METHODS:

Patients. At least 10 evaluable patients were required to complete this prospective, open-label study, Each center planned to enroll four to six patients in the study for 28 days.

Text product. Extraneal (7.5% Icodextrin) PD-2 Peritoneal Dialysis Solution with TwinBag configuration.

Dose, batch number, product code. 2.0 L 7.5% Icodextrin PD-2; 000A19G42; SPB5268

Mode of administration. Given intraperitoneally.

Duration of treatment. One exchange for twelve hours.

Assays: Total icodextrin was measured by total hydrolysis of icodextrin to glucose followed by the enzymatic determination of glucose. Free glucose was subtracted from the results of hydrolysis. Methods validation of the are shown in the separate studies.

Biological Analytes:

1. The primary study variables for assessing the pharmacokinetics of icodextrin were plasma, dialysate and urine levels of total icodextrin and icodextrin metabolites DP_2 through DP_7. Plasma samples were collected prior to the administration of study solution (Baseline), at 2, 4, 8, 12, 16, 24 hours, and at days 3, 7, 14 and 28. During the icodextrin exchange, dialysate samples were collected at 0, 2, 4, 8 and 12 hours. Dialysate samples were also collected at the end of the first, second and third post-study dwell (16, 20 and 24 hours, respectively). Urine samples were collected from a 24-hour urine collection during the in-patient stay. Pharmacokinetic analysis was performed on total icodextrin plasma concentration-time data at 0, 2, 4, 8, 12, 16 and 24 hours and at Days 3, 7, 14, 28. Analysis includes estimates of the clearance rate, the absorption rate constant, the elimination rate constant, C_{peak}, T_{max}, and AUC.
2. Urine levels of total icodextrin and icodextrin metabolites DP_2 through DP_7 were measured over a single 24-hour collection during the in-patient treatment day.

Data Analysis:

Pharmacokinetic analysis was performed on icodextrin plasma concentration-time data to estimate the clearance rate, the absorption rate constant, the elimination rate constant, C_{peak}, T_{max} and AUC. A zero-order absorption model with first-order elimination was selected as the appropriate model for this study and was used to estimate these parameters for each patient.

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RESULTS:

Thirteen patients entered the study and 11 completed the full protocol.
The absorption kinetics was described with zero-order kinetics which is consistent with convective transport mechanism of large molecular weight particles. Mean concentrations of total icodextrin in the peritoneal cavity are shown in Figure 1.

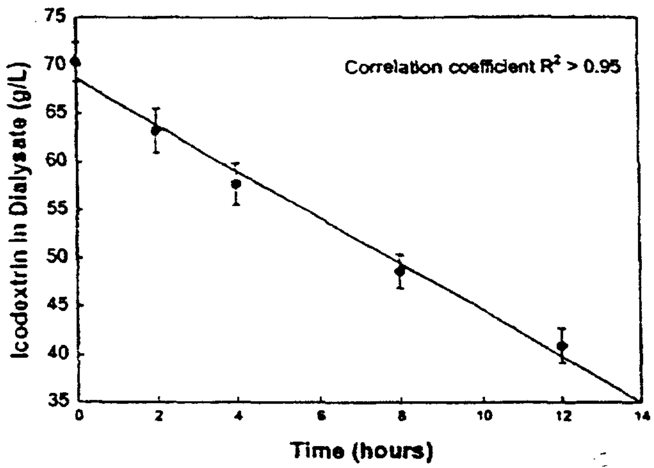


Figure 1. Mean Plasma concentration of total icodextrin in the peritoneal cavity

After the single 12 hours dwell, a median of 40% of the instilled icodextrin was absorbed. at a rate of 5 g/hr. Absorption from the peritoneal cavity during 12 hours for individual patients is described in Table 1.

Table 1. Absorption from the peritoneal cavity during 12 hours

Patient	Dose=A_t (g)	K_0 (g/hr)	Absorption %
101			
103			
104			
105			
106			
107			
201			
202			
203			
204			
301			
302			
304			
Mean	62.13	5.1776	41.42
Std Err	5.11	0.4258	3.41
Minimum			
Median	60.24	5.0204	40.16
Maximum			

Pharmacokinetics of total icodextrin in plasma was described with one-compartmental model with zero order absorption. Half-life was estimated as 14.7 hours, and clearance was 1.08 L/hr.

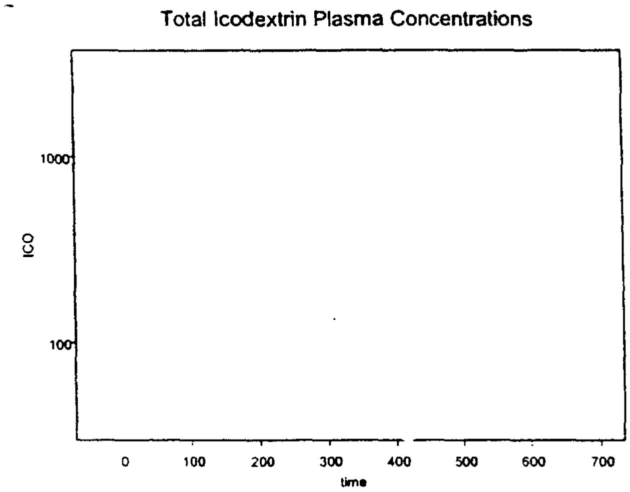
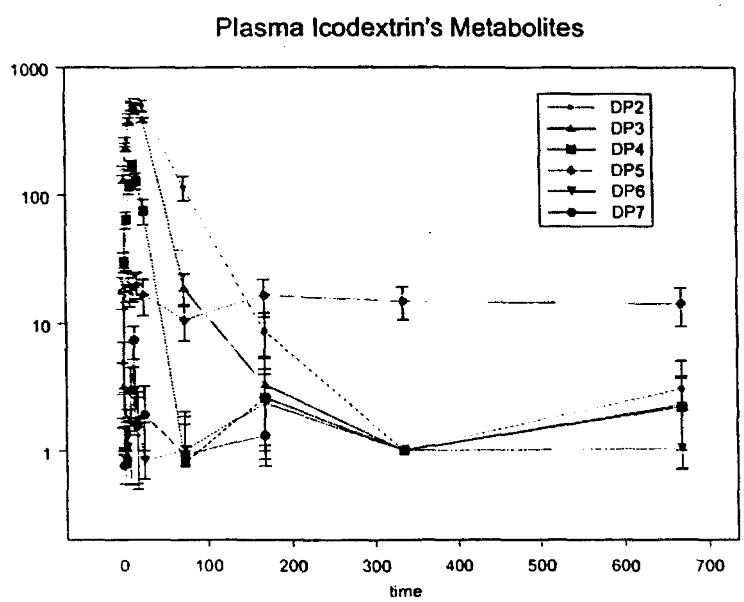


Figure 2. Total icodextrin plasma concentrations after the single 12 hours dwell

Plasma metabolite's concentrations are shown in Figure 3. The metabolites with lower molecular weight had higher plasma concentrations and progressively increased during the dwell with slow decline after the dwell. Their plasma concentrations were measurable up to 3 days post dwell. The larger metabolites levels in plasma were 30-200 fold lower than DP2.

Figure 3. Icodextrin metabolites in plasma (mean and SD values)



Mean concentrations of the metabolites in the dialysate are shown in Figure 4. The concentrations of metabolites with higher molecular weight (DP5-DP7) were higher compared to DP2-DP4 at the beginning of the dwell. During the 12 hours dwell, the concentrations of smaller polymers increased and those of the larger molecular weight declined.

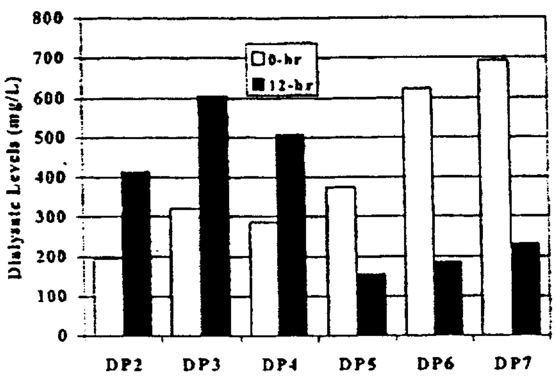
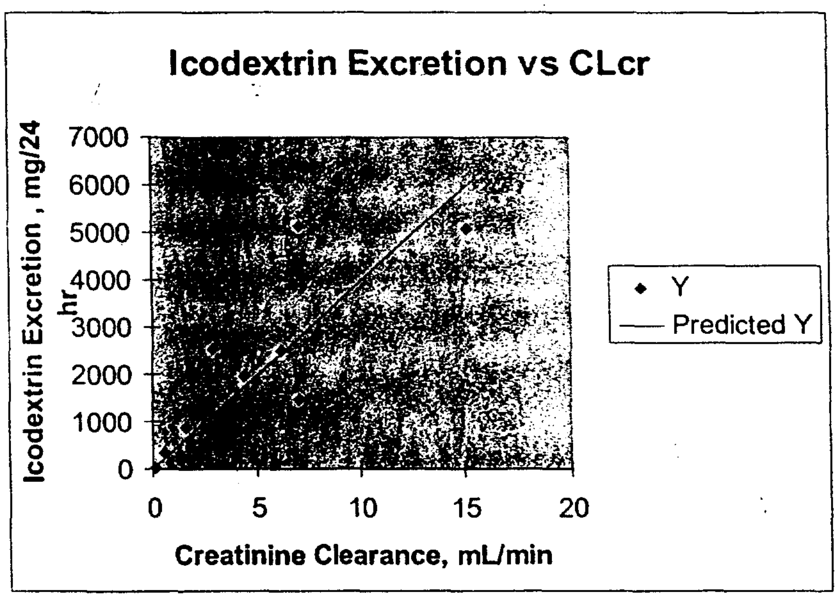


Figure 3. Mean dialysate DP2-DP7 levels at baseline and at 12 hours.

Excretion

Urinary excretion of Icodextrin was examined during the first 24 hours of the study. Four patients were anuric. The mean creatinine clearance for the other 9 patients was 5.0 ± 1.5 mL/min, and the mean urea clearance was 1.8 ± 0.73 mL/min. In the 24-hour urine collection, a mean of 2.2 ± 0.6 g of icodextrin was recovered. The icodextrin urinary excretion directly correlates with creatinine clearance. Figure 5 shows the correlation of icodextrin excretion over 24 hours vs creatinine clearance

Figure 5. Correlation of icodextrin excretion over 24 hours vs creatinine clearance



COMMENTS:

The kinetics of icodextrin absorption from the peritoneal cavity is described reasonably.

The data for total icodextrin are more complex than a one-compartmental model profile. After multiple dwells, total icodextrin plasma concentrations achieve steady state at week 2. Therefore, the reported parameter values by the sponsor are not reliable. Moreover, the parameters estimated for the bulk measurement of the sum of glucose polymers could not be interpreted physiologically. These parameters should not be cited in the Package insert.

The sponsor did not describe the pharmacokinetics of the metabolites in plasma.

BIOANALYTICAL METOD FOR TOTAL ICODEXTRIN AND ITS VALIDATION
Studies RD-94-RE-067, TR06BC99376, 10318

Method specificity is shown in Table 1.

Table 1. Method specificity for total maltodextrin

Table 1. Method Specificity for Total Maltodextrin Quantitation						
Samples from 6 Different Dialysis Patients, 200 mg/dL in Dialysate 250 mg/dL in Plasma						
Dialysate						
Sample #	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
A						
B						
C						
Mean	218	209	203	212	202	212
%RSD	4.4	7.5	5.0	4.1	2.3	4.1
% Recovery	109	105	101	106	101	106
Plasma						
Sample #	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Blank						
A-Blank						
B-Blank						
C-Blank						
Mean	264	260	254	253	248	257
%RSD	7.4	3.6	2.9	4.3	1.7	2.1
% Recovery	105	104	101	101	99	103

Precision and accuracy of the assay in the dialysate is shown in Table 2.

Table 2. Precision and accuracy of total maltodextrin in dialysate

Sample Matrix	1% Amino Acids			Spent Dialysate		
Theoretical Concentration	800 mg/dL	400 mg/dL	50 mg/dL	800 mg/dL	400 mg/dL	50 mg/dL
	Measured Concentrations (mg/dL)			Measured Concentrations (mg/dL)		
Day 1						
Intraday %RSD	0.00	0.30	2.37	0.81	2.37	3.63
% Recovery	96	97	97	99	101	115
Day 2						
Intraday %RSD	0.28	1.47	2.13	0.98	0.93	2.79
% Recovery	93	94	94	97	97	109
Day 3						
Intraday %RSD	1.76	1.33	1.14	0.83	0.58	1.02
% Recovery	102	103	101	98	100	113
Interday Summary						
Mean	775	392	49	781	397	56
Total n	9	9	9	9	9	9
%RSD	4.4	4.4	3.7	1.2	2.2	3.1
% Recovery	97	98	98	98	99	112

Precision and accuracy of the measurements of total maltodextrin in plasma is summarized in Table 3.

Maltodextrin data in plasma obtained after the assay of the triplicate on 3 separate days.

Table 3. Precision and accuracy of the measurements of total maltodextrin in plasma

	Measured Concentrations (mg/dL) (Blank Subtracted)		
Theoretical Concentration	800 mg/dL	400 mg/dL	10 mg/dL*
Day 1			
Intraday %RSD	3.23	0.80	5.09
% Recovery	98	100	113
Day 2			
Intraday %RSD	0.53	2.59	11.95
% Recovery	89	90	97
Day 3			
Intraday %RSD	0.32	1.08	6.19
% Recovery	100	101	93
Interday Summary			
Mean	765	387	10
Total n	9	9	9
%RSD	5.2	5.7	11.5
% Recovery	96	97	101

All results of the assay validation are described in Table 4.

Table 4. Summary of the assay method for total maltodextrin

Linear Range: 25-1000 mg/dL per Clinical chemistry method.
Limit of Quantitation: mg/dL per Clinical chemistry method.

Concentration (mg/dL)	n	Precision (%RSD)	Accuracy (% Recovery)
Plasma			
800	9	5.2	89-100
400	9	5.7	90-101
10	9	11.5	93-113
Dialysate			
800	9	1.2	97-99
400	9	2.2	97-101
50	9	3.1	109-115
1% Amino Acids			
800	9	4.4	93-102
400	9	4.4	94-103
50	9	3.7	94-101

Specificity: Total maltodextrin determined in dialysate and plasma from six different renal patients. Percent recoveries ranged from 101-109 in dialysate and 99-105 in plasma.

Stability: Samples stable following one or two freeze/thaw cycles.

In the year 2000, this assay was cross-validated for two available test systems (Study TP06BC99376). Finally, Study 10318 was performed to complete validation of the glucose oxidation method for total icodextrin glucose measurements in plasma, urine, and dialysate.

Precision. Within run CVs ranged from 0.0 to 13.3% for plasma, 0.9 to 16.5% for urine, and 0.0 to 3.1% for dialysate. Low icodextrin saline samples had a CV of 38.5%. Between run CVs ranged from 2.9 to 14.7% for plasma, 1.5 to 20.9% for urine, and 2.9 to 11.7% for dialysate. Low icodextrin saline samples had a CV of 36.3%.

Linearity.

Accuracy/Recovery. Recovery in saline was very poor and was excluded from this evaluation. In all matrices, over-recovery was consistently demonstrated at the lowest icodextrin concentration (15 mg/dL) and under-recovery was demonstrated at icodextrin concentrations from 50-300 mg/dL (urine and dialysate were only evaluated at 75 mg/dL). At 750 mg/dL icodextrin in all matrices, recovery was generally good. At 7500 mg/dL in dialysate, there was a tendency to over-recover.

Specificity and Stability.

The average results of supernatant samples after overnight storage in TCA were comparable to the original results since recoveries were within 10% of original results in all cases. Therefore, it is acceptable to stop the procedure after addition of 8% TCA, refrigerate the samples overnight and finish the amyloglucosidase treatment the following day.

Limits of Quantitation and Detection. The low limit of quantitation for the glucose hexokinase assay in an aqueous matrix is — mg/dL (Ref 8). The modified icodextrin method validated in this study has an inherent dilution factor of — Therefore, icodextrin can be measured in increments of — mg/dL beginning as low as — mg/dL icodextrin. However, based on recovery studies, — mg/dL icodextrin is indistinguishable from — mg/dL, indicating lack of descrimination at lower icodextrin concentrations.

When samples without icodextrin were analyzed, results ranged from — mg/dL in plasma and dialysate and — mg/dL in urine. Therefore, results below — mg/dL cannot be distinguished from —

COMMENTS:

The method of total icodextrin assay is acceptable for accuracy, recovery, and LOQ. However, this method is lacking the specificity because the obtained measurements do not belong to the specific molecular entity but are the sum of different glucose polymers.

BIOANALYTICAL METOD FOR ICODEXTRIN METABOLITES AND ITS VALIDATION

Studies RD-RE-B-013, RD-95-RE-134, RD-98-010, RD-94-RE-074

Icodextrin metabolites were measured by [redacted]

The assay was validated in plasma (Study RD-94-RE-074). The summary of the assay validation for icodectrin metabolites in plasma is shown in Table 1.

Table 1. Validation of icodextrin metabolites assay

Maltodextrin Metabolite Method Summary

Range*: 0.1-10 µg/ml
Limit of Detection: 0.05 µg/ml
Limit of Quantitation*: µg/ml DP2-DP7
(The actual limit for samples diluted 1:100 is 10 µg/ml)

Concentration (µg/ml)	n	Precision (%RSD)	Accuracy (% Recovery)
7.5			
DP2	12	1.2	99-100
DP3	12	1.3	99-101
DP4	12	1.4	99-101
DP5	12	1.6	98-101
DP6	12	1.9	97-102
DP7	12	2.7	99-103
1.0			
DP2	12	5.3	97-105
DP3	12	2.8	102-104
DP4	12	3.0	97-103
DP5	12	2.8	97-104
DP6	12	2.4	97-105
DP7	12	3.0	98-105
0.1			
DP2	12	15.4	92-115
DP3	12	6.2	105-117
DP4	12	17.2	81-103
DP5	12	10.8	99-109
DP6	12	12.9	87-92
DP7	12	26.7	91-105

Specificity*: DP2-DP7 quantitated in spent dialysate from six different dialysis patients.
Stability ESRD plasma samples containing amylase inhibitor are stable at:
- room temperature up to 2 hours*
- following one or two freeze-thaw cycles*.
- following dilution/filtration, refrigerated for up to 72 hour*.

ESRD plasma samples are stable:
- for one year following storage at - 70 °C with the possible exception of DP2 and DP5.

Validation of the assay for metabolites of icoextrin in urine (Study RD-98-RE-010) is shown in Table 16

Data summary of method precision, and accuracy in Urine samples

Table 16: Icodextrin metabolites validation summary in urine samples

Limit of Quantitation: μg/ml G3-G7

Concentration (μg/ml)	Metabolite	n.	Precision (% RSD)	Accuracy * (% Recovery)	Accuracy † ** (% Recovery)
LSPK	G2	12	19.3	[redacted]	[redacted]
(10 μg/ml)	G3	12	6.1	93.6 -127.1	93.6 - 119.5
	G4	12	15.1	94.8 -103.8	94.2 - 113.0
	G5	9	8.8	115.1 - 118.4	124.0 - 127.3
	G6	12	18.7	99.6 - 112.6	99.6 - 122.5
	G7	12	6.1	89.7 - 91.4	89.7 - 105.7
MSPK	G2	12	7.0	104.4 - 124.2	104.4 - 120.2
(100 μg/ml).	G3	12	4.0	103.0 - 106.7	103.2 - 110.3
	G4	12	1.6	99.9 - 105.4	101.6 - 105.4
	G5	9	3.0	97.9 - 101.9	100.4 - 103.6
	G6	12	3.1	95.9 - 99.3	95.9 - 100.6
	G7	12	3.0	92.6 - 94.1	91.8 - 93.9
HSPK	G2	12	4.6	103.0 - 108.0	103.0 - 108.3
(750 μg/ml)	G3	12	4.6	103.5 - 104.7	104.5 - 109.7
	G4	12	3.3	102.3 - 102.8	100.8 - 104.4
	G5	12	7.1	97.9 - 104.0	97.9 - 109.8
	G6	12	9.0	88.8 - 98.5	88.8 - 101.3
	G7	12	9.4	88.6 - 97.2	88.6 - 98.2

COMMENTS:
The assay method for metabolites is acceptable.

Validation of the assay for metabolites of icoextrin in spent dialysate (Study RD-98-RE-010) is shown in Table 15.

Data summary of method precision, and accuracy in human spent dialysate

Table 15: Icodextrin metabolites validation summary in human spent dialysate

Limit of Quantitation: µg/ml G2-G7
(the actual limit for samples diluted 1:100 is 10 µg/ml)

Concentration (µg/ml)	Metabolite	n	Precision (% RSD)	Accuracy * (% Recovery)	Accuracy † ** (% Recovery)
LSPK (10 µg/ml)	G2	12	3.2	77.9 - 89.0	88.5 - 99.5
	G3	12	6.8	82.0 - 104.8	93.9 - 127.4
	G4	12	7.0	96.2 - 107.5	113.3 - 125.7
	G5	12	6.9	91.0 - 106.9	112.6 - 130.4
	G6	12	3.2	96.3 - 101.6	109.2 - 116.0
	G7	12	6.1	80.2 - 98.6	97.9 - 128.8
MSPK (100 µg/ml)	G2	12	1.4	98.6 - 100.8	102.2 - 104.8
	G3	12	1.1	100.2 - 102.2	108.9 - 111.3
	G4	12	0.8	101.4 - 102.7	106.6 - 108.1
	G5	12	5.4	96.4 - 103.1	100.2 - 112.2
	G6	12	5.0	96.8 - 101.6	102.6 - 109.6
	G7	12	4.0	97.7 - 100.8	102.2 - 106.9
HSPK (750 µg/ml)	G2	12	4.3	100.3 - 104.2	106.2 - 113.8
	G3	12	5.3	100.4 - 106.5	112.0 - 119.6
	G4	12	5.3	99.9 - 106.7	107.5 - 116.1
	G5	12	8.7	99.6 - 102.2	104.2 - 125.5
	G6	12	6.2	97.3 - 99.6	100.6 - 111.9
	G7	12	6.7	98.2 - 100.9	97.9 - 112.6

STUDY RD-97-CA-130

A Study to Evaluate the Safety and Efficacy of 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Continuous Ambulatory Peritoneal Dialysis

Study ID: RD-99-CA-130 Volume: 1.16

Principal Investigator's information is referred to Appendix 16.1.4, which is not available for review. The sponsor's information is provided:

Title	Name	Phone	Fax	Affiliation
Medical Director	Marsha Wolfson, MD	847-473-6343	847-473-6923	Baxter Healthcare Corp. Renal Division Clinical Affairs McGaw Park, IL 60085
Clinical Program Manager	Tricia Hagen	847-473-6074	847-473-6923	Baxter Healthcare Corp. Renal Division Clinical Affairs McGaw Park, IL 60085
Senior Research Scientist, Clinical Statistician	Francis G. Ogrinc, Ph.D.	847-473-6829	847-473-6923	Baxter Healthcare Corp. CRTS/Applied Statistics Rte. 120 & Wilson Rd. Round Lake, IL 60073

Objectives:	The purpose of this study was to evaluate the efficacy and safety of a peritoneal dialysis solution containing 7.5% Icodextrin as the long dwell exchange solution to replace the use of Dianeal® PD-2 or PD-4 Peritoneal Dialysis Solution with 2.5% dextrose in CAPD patients.

METHODS:

<u>Patients.</u> At least 144 evaluable patients were required to complete this prospective, randomized, double blind, parallel group, active control study. Each center planned to randomize 6-8 patients in the study for 4 weeks.

<u>Text product.</u> Extraneal (7.5% Icodextrin) PD-2 Peritoneal Dialysis Solution with TwinBag of UltraBag configuration.

<u>Dose, batch number, product code.</u>

2.0 L 7.5% Icodextrin PD-2; AX2020-C378414, JX0005-W8DO6T1
2.5 L 7.5% Icodextrin PD-2; AX2027-C380105, JX0008-W8DO7T1

<u>Mode of administration.</u> Given intraperitoneally.

Duration of treatment. One exchange per day for the long dwell.

Control Solution: 2.0L or 2.5 L Dianeal PD-2 or PD-4 Peritoneal Dialysis Solution with 1.5% Dextrose in the TwinBag of UltraBag configuration.

Dose, batch number, product code.

2.0 L 2.5% dextrose Dianeal PD-2; AX2022-C377846, JX0002-W8DO8T0
2.5 L 2.5% dextrose Dianeal PD-2; AX2028-C377853, JX0004-W8DO8T1

Assays: Total icodextrin was measured by total hydrolysis of icodextrin to glucose followed by the enzymatic determination of glucose. Free glucose was subtracted from the results of hydrolysis.

Icodextrin metabolites were measured by [redacted]

Biological Analytes:

Total Icodextrin, maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), maltopentaose (DP_5), maltohexaose (DP_6) and maltoheptaose (DP_7) plasma levels were measured at baseline and at the end of the study, to confirm that a steady state plasma level is reached.
Monitoring clinically meaningful changes from baseline: laboratory evaluations (hematology with differential, serum electrolytes, serum urea nitrogen, creatinine and liver enzymes), and fluid imbalances (i.e., edema, dehydration).

Statistical Methods:

Repeated measures analysis of variance, analysis of covariance, Pearson's Chi-Square test, Fisher's exact test, Student t-test and Wilcoxon rank sum test. Statistical significance is defined as p < or = 0.05.

RESULTS

Pharmacokinetic data include information on the plasma steady state levels and the elimination of icodextrin.

Steady state total icodextrin plasma concentrations and maltose were calculated at week 2 as 5.08 ± 0.21 g/L, and 0.85 ± 0.03 g/L, respectively.

Metabolite plasma concentrations are shown in Table 14.3.4-5. The highest concentration were achieved for DP2 and DP 3, about .8 g/L, followed by DP4 (.3 g/L. The large polymers had low plasma concentrations, ranging from 0.022 (DP7) to 0.036 (DP5).

Table 14.3.4-5 (Page 1 of 1)
Plasma Levels for Icodextrin and Its Metabolites -- Means and Mean Changes at Each vis_num

		Treatment	Baseline@	Data						Change from Baseline @						
Metabolite	Visit	Group	Mean	N	Mean	Std Err	Min	Median	Max	Mean	Std Err	p W/in	Min	Median	Max	p Betw
ICODEXTRIN (MG/L)	Baseline	Control		84	43.929	3.791		40.00								0.100
	(Week 0)	Icodextrin		89	157.753	66.725		40.00								
	Week 4	Control	42.716	82	48.171	6.274		40.00		5.679	5.932	0.341		0.00		<0.001
		Icodextrin	38.734	80	5082.375	212.838		5125.00		5072.532	213.153	<0.001		5110.00	1	
DP2 (MG/L)	Baseline	Control		84	1.421	0.571		0.00								0.096
	(Week 0)	Icodextrin		89	24.173	13.189		0.00								
	Week 4	Control	1.474	82	0.437	0.313		0.00		-1.298	0.622	0.040		0.00		<0.001
		Icodextrin	0.841	80	848.302	31.698		844.28		849.547	31.976	<0.001		854.01		
DP3 (MG/L)	Baseline	Control		84	1.008	0.477		0.00								0.105
	(Week 0)	Icodextrin		89	20.100	11.373		0.00								
	Week 4	Control	1.045	82	0.000	0.000		0.00		-1.045	0.495	0.038		0.00		<0.001
		Icodextrin	0.587	80	812.866	31.281		819.91		815.820	31.485	<0.001		819.58		
DP4 (MG/L)	Baseline	Control		84	0.141	0.141		0.00								0.142
	(Week 0)	Icodextrin		89	6.938	4.474		0.00								
	Week 4	Control	0.146	82	0.000	0.000		0.00		-0.146	0.146	0.320		0.00		<0.001
		Icodextrin	0.281	80	320.872	16.041		313.77		322.606	16.145	<0.001		316.02		
DP5 (MG/L)	Baseline	Control		84	0.000	0.000		0.00								0.175
	(Week 0)	Icodextrin		89	1.003	0.716		0.00								
	Week 4	Control	0.000	82	0.000	0.000		0.00		0.000	0.000	.		0.00		<0.001
		Icodextrin	0.467	80	36.669	2.850		38.34		36.666	2.912	<0.001		38.85		
DP6 (MG/L)	Baseline	Control		84	0.000	0.000		0.00								0.333
	(Week 0)	Icodextrin		89	0.243	0.243		0.00								
	Week 4	Control	0.000	82	0.000	0.000		0.00		0.000	0.000	.		0.00		<0.001
		Icodextrin	0.000	80	17.616	2.329		0.00		17.839	2.348	<0.001		0.00		
DP7 (MG/L)	Baseline	Control		84	0.283	0.283		0.00								0.998
	(Week 0)	Icodextrin		89	0.285	0.285		0.00								
	Week 4	Control	0.294	82	0.000	0.000		0.00		-0.294	0.294	0.320		0.00		<0.001
		Icodextrin	0.000	80	22.882	2.753		21.97		23.172	2.773	<0.001		22.20		

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

COMMENTS

Total icodextrin and its metabolites concentrations in plasma increased by week 4. The levels of DP6 and DP7 at week 4 were 5-10 fold larger than after the end of the single 12 hours dwell.

STUDY RD-97-CA-131

A Study to Evaluate the Safety of 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Peritoneal Dialysis in North America

Study ID: RD-97-CA-131 Volume: 1.16

Principal Investigator's information is referred to Appendix 16.1.4, which is not available for review. The sponsor's information is provided:

Title	Name	Phone / Fax	Affiliation
Medical Director	Marsha Wolfson, MD, FACP	847-473-6343 847-473-6923	Baxter Healthcare Corp. Renal Division Clinical Affairs McGaw Park, IL 60085
Clinical Program Manager	Tricia Hagen	847-473-6074 847-473-6923	Baxter Healthcare Corp. Renal Division Clinical Affairs McGaw Park, IL 60085
Senior Research Scientist, Clinical Statistician	Francis G. Ogrinc, PhD	847-473-6829 847-473-6923	Baxter Healthcare Corp. CRTS/Applied Statistics Rte. 120 & Wilson Rd. Round Lake, IL 60073

Objectives:	The purpose of this study was to evaluate the safety of using a peritoneal dialysis solution containing 7.5% icodextrin as the long dwell solution to replace the current use of Dianeal® PD-2 or PD-4 Peritoneal Dialysis Solution with 2.5% Dextrose (2.27% glucose) in PD patients in North America.

METHODS:

Patients. At least 300 evaluable patients were required (150 patients in the icodextrin treatment group) to complete this prospective, randomized (2:1), double blind, parallel group, active control study. Approximately 40 centers were to randomize 6-8 patients in the study for 12 months (52 weeks).

Text product. Extraneal (7.5% Icodextrin) PD-2 Peritoneal Dialysis Solution

Dose, batch number, product code.
2.0 L 7.5% Icodextrin PD-2; AX2020-C378414, JX0005-W8DO6T1
2.5 L 7.5% Icodextrin PD-2; AX2027-C380105, JX0008-W8DO7T1
C414813-C414821; C426578-C425660; W8D07B3KX-W8D06B2

Mode of administration. Given intraperitoneally.

Duration of treatment. One exchange per day for the long dwell for 52 weeks.
Control Solution: 2.0L or 2.5 L Dianeal PD-2 or PD-4 Peritoneal Dialysis Solution with 1.5% Dextrose in the TwinBag of UltraBag configuration.
Dose, batch number, product code.
2.0 L 2.5% dextrose Dianeal PD-2; AX2032-C379846, JX0003-W8DO8T0
2.5 L 2.5% dextrose Dianeal PD-2; AX2058-C379853, JX0006-W8DO8T1

Assays: Total icodextrin was measured by total hydrolysis of icodextrin to glucose followed by the enzymatic determination of glucose. Free glucose was subtracted from the results of hydrolysis.

Icodextrin metabolites were measured by

Biological Analytes:

The plasma levels for total icodextrin, maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), maltopentaose (DP_5), maltohexaose (DP_6), and maltoheptaose (DP_7), as collected over time, were evaluated by a) paired t-tests to compare each Follow-up time point to Baseline and b) repeated measures analyses to establish that the plasma levels reached a steady state and remained at those levels over time.

RESULTS

Two hundred eighty-seven patients have completed this study.
Pharmacokinetic data includes the information on plasma steady state levels and elimination of icodextrin. Steady state total icodextrin plasma concentrations were between 4.8 and 5.03 g/L at weeks 4, 13, 26, 39, and 52. In the control group maltose was measured in plasma as 0.85 ± 0.03 g/L. Metabolite plasma concentrations were measured as well. The highest concentrations were achieved for DP2 and DP3, about 0.8 g/L, followed by DP4 at 0.3 g/L. The large polymers had low plasma concentrations, ranging from 0.022 (DP7) to 0.036 (DP5). Table 1 lists the plasma concentrations data for icodextrin and control groups.

Table 1. Mean Icodextrin plasma concentrations

Visit	Treatment Group	Baseline Mean[a]	N	Mean	Std Error
Baseline	Control		110	42.545	3.322
(Week 0)	Icodextrin		173	41.850	2.692
Week 4	Control	44.590	62	49.355	7.845
	Icodextrin	36.000	66	5030.758	208.102
Week 13	Control	43.404	94	45.319	3.790
	Icodextrin	43.429	141	5023.688	157.881
Week 26	Control	43.704	81	175.556	86.858
	Icodextrin	41.575	128	4758.750	167.924
Week 39	Control	41.571	70	38.857	3.727
	Icodextrin	42.545	111	5074.595	193.011
Week 52	Control	40.952	63	38.571	2.914
	Icodextrin	40.096	104	4997.596	206.258

[a] Baseline means are calculated from patients with observations at each respective visit.

The results of plasma measurements of metabolites are shown in Figure 1.

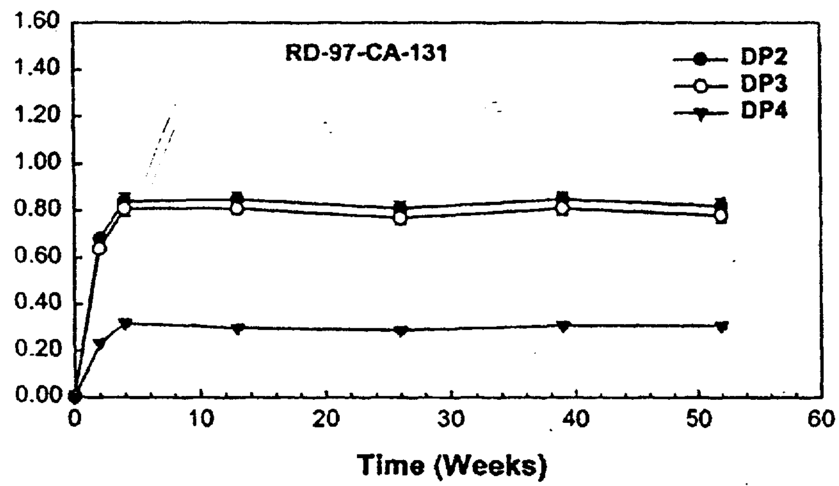


Figure 1. DP2, DP3, and DP4 plasma concentrations at steady state.

Analysis of variance with repeated measures compared the data obtained at week 4 and week 52 for total icodextrin and metabolites. The differences are reported as statistically insignificant.

COMMENTS:

Steady state plasma concentrations of icodextrin measured up to week 52 were in the range of the previously reported values for the 4-week clinical trial. The metabolite plasma concentrations were not summarized statistically. The results were shown graphically.

An attempt was made to evaluate the effects gender, site, race and diabetic status on treatment using SAS. The influence of these covariates on the pharmacokinetics of icodextrin and/or its metabolites was not assessed.

STUDY PRO-RENAL-REG-035

A Study to Evaluate the Safety and Efficacy of 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Automated Peritoneal Dialysis (APD)

Study ID: PRO-RENAL-REG-035 **Volume:** 1.17

Investigators and study centres:	Prof. Dr. R. Brunkhorst / — Medizinische Hochschule Hannover Nephrologische Abt. Carl-Neuberg-Str 1., 30625 Hannover, Germany Prof. Dr. C. Wanner / — Medizinishen Universität Klinik Nephrologische Abt. Josef - Schneider Str. 2, 97080 Würzburg, Germany Prof. Dr. B. Grabensee / — Medizinische Einrichtungen der Heinrich-Heine-Universität Düsseldorf Medizinische Klinik und Poliklinik, Klinik für Nephrologie Moorenstr. 5, 40225 Düsseldorf, Germany Dr. B. Faller / — Hôpital Louis Pasteur, Service de Néphrologie et de Dialyse Avenue de la Liberté 39, 68024 Colmar Cedex, France Dr. P. Freida Hôpital Louis Pasteur, Service de Néphrologie / Dialyse 46, rue du val de Saire, 50102 Cherbourg, France Dr. C. Verger Hôpital René Dubos, Unité de Dialyse Péritonéale 6 Avenue de L'Ile-de-France, 95301 Pontoise, France Dr. D. Struijk Academic Medical Center, Department of Nephrology Meibergdreef 9, 1105 AZ Amsterdam Zuidoost, The Netherlands Prof. Dr. Y. Vanrenterghem / — A.Z. K.U.L. Gasthuisberg, Department of Nephrology Herestraat 49, 3000 Leuven, Belgium

Objectives:	**The purpose of this study was to compare the safety and efficacy of a peritoneal dialysis solution containing 7.5% icodextrin as a long dwell exchange solution with the 2.27% glucose solution (Dianeal® PD4) in patients treated with automated peritoneal dialysis (APD).**

METHODS:

Patients. Thirty two evaluable patients were to complete this prospective, randomized, open-label, parallel group, active control study. Patients participated in this study for 4 months (16 weeks). The study included a 2-week baseline period followed by a 12-week treatment period and finally a 2 week follow up period.

Text product. Extraneal (7.5% Icodextrin) PD-2 Peritoneal Dialysis Solution in a single bag configuration.

Dose, batch number, product code.
2.0 L 7.5% Icodextrin PD-2; EUBX0332R, 96K23G30

Mode of administration. Given intraperitoneally, using system.

Duration of treatment. Single day-time dwell administered for 16 weeks.

Control Solution: 2.0L or 2.5 L Dianeal PD-4 Peritoneal Dialysis Solution with 2.27% glucose in single bag configuration.

Dose, batch number, product code.
2.0 L bag SPB9727RL

Assays: Total icodextrin was measured by total hydrolysis of icodextrin to glucose followed by the enzymatic determination of glucose. Free glucose was subtracted from the results of hydrolysis.

Icodextrin metabolites were measured by

Biological Analytes:

Total Icodextrin, maltose (DP2), maltotriose (DP3), maltotetraose (DP4), maltopentaose (DP5), maltohexaose (DP6), and maltoheptaose (DP7) plasma levels measured prior to, during, and after treatment in order to confirm that a steady state plasma level is reached and that levels return to baseline upon discontinuation of Icodextrin (i.e., during the follow-up period).

RESULTS

Thirty nine patients have completed this study.
Pharmacokinetic data includes the information on the plasma steady state levels and the elimination of icodextrin. Steady state total icodextrin plasma concentrations were calculated at weeks –1, 1, 6, 12, 13 and 14. The results are shown in Table 1.

Table 1. Total plasma icodextrin (mg/L)

Visit	Treatment Group	Baseline Mean	Data Mean	Data Std Error	Change from baseline Mean	Change from baseline Std Error	p W/in *	p Betw **
Baseline Week -1	Control		64.4	6.5				0.797
	Icodextrin		61.6	8.9				
Week 1	Control	64.4	57.2	6.9	-7.2	10.3	0.492	<0.001
	Icodextrin	61.6	6186.8	399.0	6125.3	399.9	<0.001	
Week 6	Control	63.5	58.2	7.7	-5.3	5.0	0.306	<0.001
	Icodextrin	62.4	6431.2	482.1	6368.8	483.1	<0.001	
Week 12	Control	60.0	68.1	10.2	8.1	10.8	0.464	<0.001
	Icodextrin	64.4	6336.9	475.4	6272.5	478.0	<0.001	
Follow-up Week 13	Control	60.0	64.4	10.7	4.4	10.0	0.669	0.001
	Icodextrin	64.4	597.5	151.0	533.1	147.9	0.003	
Follow-up Week 14	Control	58.7	60.0	8.7	1.3	7.6	0.862	0.180
	Icodextrin	64.4	83.8	13.8	19.4	12.1	0.130	

In the control group maltose was measured in plasma, Table 2.

Table 2. Plasma maltose concentrations

Visit	Treatment Group	Baseline Mean	Data Mean	Data Std error	Change from baseline Mean	Change from baseline Std Error	p W/in *	p Betw **
Baseline Week -1	Control		0.0	0.0				0.337
	Icodextrin		1.6	1.6				
Week 1	Control	0.0	0.0	0.0	0.0	0.0	.	<0.001
	Icodextrin	1.6	1112.5	59.4	1110.8	58.9	<0.001	
Week 6	Control	0.0	1.3	1.3	1.3	1.3	0.332	<0.001
	Icodextrin	1.8	1106.9	73.2	1105.1	72.6	<0.001	
Week 12	Control	0.0	0.0	0.0	0.0	0.0	.	<0.001
	Icodextrin	1.9	1056.5	78.7	1054.5	77.9	<0.001	
Follow-up Week 13	Control	0.0	0.0	0.0	0.0	0.0	.	0.002
	Icodextrin	1.9	88.5	25.5	86.6	25.8	0.004	
Follow-up Week 14	Control	0.0	0.0	0.0	0.0	0.0	.	0.326
	Icodextrin	1.9	0.7	0.7	-1.3	2.1	0.557	

**: p W/in= p-value for significant mean change from baseline within treatment group (paired t-test analysis)*
***: p Betw= - At baseline (Wk -1): p-value for significant differences across treatment group means (analysis of variance)*
- At Post-baseline visits (Treatment: Wks 1,6,12; Follow-Up: Wk 13, 14): p-value for significant differences across treatment groups for mean changes (analysis of covariance)

Plasma levels of icodextrin and its metabolites were elevated within the icodextrin group. Mean changes were significant at weeks 1,6, and 12. One week after the treatment was discontinued, the mean values were still significantly higher that baseline values (p=0.003). By week 14 these changes were not statistically significant. The findings were similar for the metabolites of icodextrin (Table 3).

Table 3. Plasma Icodextrin and its metabolites concentrations

Lab Assay	Visit	Treatment Group	Baseline@ Mean	Data N	Data Mean	Data Std Err	Data Min	Data Max	Change from Baseline @ Mean	Change from Baseline @ Std Err	Change from Baseline @ p W/in	Change from Baseline @ Min	Change from Baseline @ Max	p Betw
Total Plasma Icodextrin (mg/L)	Baseline (Week -1)	Control		18	64.444	6.479								0.797
		Icodextrin		19	61.579	8.861								
	Week 1	Control	64.444	18	57.222	6.898			-7.222	10.284	0.492			<0.001
		Icodextrin	61.579	19	6186.842	399.008			6125.263	399.888	<0.001			
	Week 6	Control	63.529	17	58.235	7.681			-5.294	5.009	0.306			<0.001
		Icodextrin	62.353	17	6431.176	482.047			6368.824	483.059	<0.001			
	Week 12	Control	60.000	16	68.125	10.215			8.125	10.810	0.464			<0.001
		Icodextrin	64.375	16	6336.875	475.418			6272.500	478.020	<0.001			
	Week 13 (Foll/Up)	Control	60.000	16	64.375	10.645			4.375	10.040	0.669			0.001
		Icodextrin	64.375	16	597.500	151.031			533.125	147.884	0.003			
	Week 14 (Foll/Up)	Control	58.667	15	60.000	8.674			1.333	7.551	0.862			0.180
		Icodextrin	64.375	16	83.750	13.750			19.375	12.092	0.130			
Plasma G2 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								0.337
		Icodextrin		19	1.620	1.620								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	1.620	19	1112.463	59.383			1110.843	58.855	<0.001			
	Week 6	Control	0.000	17	1.271	1.271			1.271	1.271	0.332			<0.001
		Icodextrin	1.810	17	1106.891	73.244			1105.081	72.595	<0.001			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	1.923	16	1056.457	78.689			1054.534	77.925	<0.001			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.002
		Icodextrin	1.923	16	88.536	25.518			86.613	25.803	0.004			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			0.326
		Icodextrin	1.923	16	0.674	0.674			-1.249	2.080	0.557			

Table 3. Plasma Icodextrin and its metabolites concentrations

Lab Assay	Visit	Treatment Group	Baseline@ Mean	Data N	Data Mean	Data Std Err	Data Min	Data Max	Change from Baseline @ Mean	Change from Baseline @ Std Err	Change from Baseline @ p W/in	Change from Baseline @ Min	Change from Baseline @ Max	p Betw
Total Plasma Icodextrin (mg/L)	Baseline (Week -1)	Control		18	64.444	6.479								0.797
		Icodextrin		19	61.579	8.861								
	Week 1	Control	64.444	18	57.222	6.898			-7.222	10.284	0.492			<0.001
		Icodextrin	61.579	19	6186.842	399.008			6125.263	399.888	<0.001			
	Week 6	Control	63.529	17	58.235	7.681			-5.294	5.009	0.306			<0.001
		Icodextrin	62.353	17	6431.176	482.047			6368.824	483.059	<0.001			
	Week 12	Control	60.000	16	68.125	10.215			8.125	10.810	0.464			<0.001
		Icodextrin	64.375	16	6336.875	475.418			6272.500	478.020	<0.001			
	Week 13 (Foll/Up)	Control	60.000	16	64.375	10.645			4.375	10.040	0.669			0.001
		Icodextrin	64.375	16	597.500	151.031			533.125	147.884	0.003			
	Week 14 (Foll/Up)	Control	58.667	15	60.000	8.674			1.333	7.551	0.862			0.180
		Icodextrin	64.375	16	83.750	13.750			19.375	12.092	0.130			
Plasma G2 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								0.337
		Icodextrin		19	1.620	1.620								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	1.620	19	1112.463	59.383			1110.843	58.855	<0.001			
	Week 6	Control	0.000	17	1.271	1.271			1.271	1.271	0.332			<0.001
		Icodextrin	1.810	17	1106.891	73.244			1105.081	72.595	<0.001			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	1.923	16	1056.457	78.689			1054.534	77.925	<0.001			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.002
		Icodextrin	1.923	16	88.536	25.518			86.613	25.803	0.004			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			0.326
		Icodextrin	1.923	16	0.674	0.674			-1.249	2.080	0.557			

Table 3, continued

Lab Assay	Visit	Treatment Group	Baseline@ Mean	Data N	Data Mean	Data Std Err	Data Min	Data Max	Change from Baseline @ Mean	Change from Baseline @ Std Err	Change from Baseline @ p W/in	Change from Baseline @ Min	Change from Baseline @ Max	p Betw
Plasma G3 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								.
		Icodextrin		19	0.000	0.000								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	19	1065.015	47.559			1065.015	47.559	<0.001			
	Week 6	Control	0.000	17	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	17	1067.867	56.940			1067.867	56.940	<0.001			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	16	1038.565	69.398			1038.565	69.398	<0.001			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.052
		Icodextrin	0.000	16	27.672	13.675			27.672	13.675	0.061			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			
Plasma G4 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								.
		Icodextrin		19	0.000	0.000								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	19	368.240	31.139			368.240	31.139	<0.001			
	Week 6	Control	0.000	17	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	17	340.346	37.487			340.346	37.487	<0.001			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	16	334.635	32.619			334.635	32.619	<0.001			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.325
		Icodextrin	0.000	16	1.652	1.652			1.652	1.652	0.333			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			

Table 3, continued

Lab Assay	Visit	Treatment Group	Baseline@ Mean	Data N	Data Mean	Data Std Err	Data Min	Data Max	Change from Baseline @ Mean	Change from Baseline @ Std Err	Change from Baseline @ p W/in	Change from Baseline @ Min	Change from Baseline @ Max	p Betw
Plasma G5 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								.
		Icodextrin		19	0.000	0.000								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			0.014
		Icodextrin	0.000	19	12.616	4.741			12.616	4.741	0.016			
	Week 6	Control	0.000	17	0.000	0.000			0.000	0.000	.			0.020
		Icodextrin	0.000	17	12.728	5.198			12.728	5.198	0.026			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			<0.001
		Icodextrin	0.000	16	17.643	3.826			17.643	3.826	<0.001			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			
Plasma G6 (mg/L)	Baseline (Week -1)	Control		18	0.000	0.000								.
		Icodextrin		19	0.000	0.000								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			0.098
		Icodextrin	0.000	19	5.512	3.155			5.512	3.155	0.098			
	Week 6	Control	0.000	17	0.000	0.000			0.000	0.000	.			0.090
		Icodextrin	0.000	17	6.146	3.517			6.146	3.517	0.100			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.082
		Icodextrin	0.000	16	5.077	2.818			5.077	2.818	0.092			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			

Table 3, continued

Lab Assay	Visit	Treatment Group	Baseline@ Mean	Data N	Data Mean	Data Std Err	Data Min	Data Max	Change from Baseline @ Mean	Change from Baseline @ Std Err	Change from Baseline @ p W/In	Change from Baseline @ Min	Change from Baseline @ Max	p Betw
Plasma G7 (mg/l.)	Baseline (Week -1)	Control		18	0.000	0.000					.			.
		Icodextrin		19	0.000	0.000								
	Week 1	Control	0.000	18	0.000	0.000			0.000	0.000	.			0.063
		Icodextrin	0.000	19	6.987	3.540	[redacted]	[redacted]	6.987	3.540	0.064	[redacted]	[redacted]	
	Week 6	Control	0.000	17	0.000	0.000			0.000	0.000	.			0.094
		Icodextrin	0.000	17	6.703	3.887			6.703	3.887	0.104			
	Week 12	Control	0.000	16	0.000	0.000			0.000	0.000	.			0.037
		Icodextrin	0.000	16	6.812	3.120			6.812	3.120	0.045			
	Week 13 (Foll/Up)	Control	0.000	16	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			
	Week 14 (Foll/Up)	Control	0.000	15	0.000	0.000			0.000	0.000	.			.
		Icodextrin	0.000	16	0.000	0.000			0.000	0.000	.			

The highest concentration were achieved for DP2 and DP3 (about 1.1 g/L) followed by DP4 (0.34 g/L). The large polymers had low plasma concentrations, ranged from 0.006 (DP7) to 0.012 (DP5).

COMMENTS:
Steady state total icodextrin and its metabolites plasma concentrations in the APD setting were similar to the data reported previously from other studies with the CAPD setting. In the short day-time dwells, the low molecular weight polymers have slightly higher, and plasma concentrations of high molecular weight polymers have lower mean plasma concentrations compared to the plasma levels obtained with the use of long dwells. Nevertheless, short dwells appeared to be safe for use.

STUDY ML/IB 002

Addition of Insulin to Dextrin 20 and Glucose CA Peritoneal Dialysis Solutions

Study ID: ML/IB 002 **Volume:** 1.22
Study performed from March to April 1991.

Principal Investigator information:

INVESTIGATORS

C.D. Mistry MD MRCP
Cardiff Royal Infirmary
Newport Road
Cardiff. CF2 1SZ

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The objective of this randomised open crossover study was to compare the rate of absorption of insulin from the peritoneum with CAPD fluid containing 7.5% Dextrin 20 or 1.36% glucose as the osmotic agents.

METHODS:

Study Design. An open-label, randomized, controlled crossover study in 6 patients. At two separate visits, eligible patients received in random order a 1.36% glucose CAPD bag and Dextrin 20 (7.5%) CAPD bag, both containing their usual dose of insulin, for a 6 hours dwell.

Text product. Dextrin 20 was manufactured and supplied by M.L.Laboratories plc.

Batch number, product code. Not available.

Mode of administration. Given intraperitoneally.

Duration of treatment. One exchange per day for 6 hours dwell.

Control Solution: 1.365% glucose solution.

Batch number, product code. Not available

Assays: Not described

Statistical Methods:
The parameters that were analyzed were glucose and insulin plasma levels, and glucose and insulin CAPD fluid levels. The comparisons were made using standard methods for the analysis of quantitative variables in two-period crossover studies. Input and output files were not available for review. These techniques allowed an investigation of the effects due to period and to carry-over of the previous treatment, the test for carry-over effect being performed was at the 10% significance level. A comparison of the treatments was carried out by comparison of treatment means, adjusted for the effect due to period.
Insulin absorption rate from the peritoneum to blood was calculated.
Blood samples were taken during the 6 hours of the dwell, bag weights were measured to estimate the net ultrafiltration.

RESULTS:

The differences in insulin levels in both plasma and dialysate fluid were not statistically significant ($p= 0.67$ and $p= 0.22$, respectively). Figures 1 and 2 show the plasma and CAPD liquid mean levels of insulin during the dwell. There was a large difference in glucose levels in plasma and dialysate in both treatments.

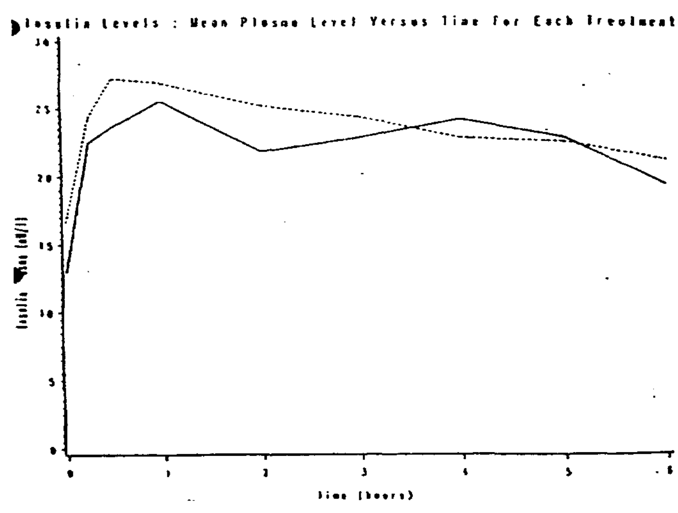

Figure 1. Mean plasma concentration of insulin in both treatments

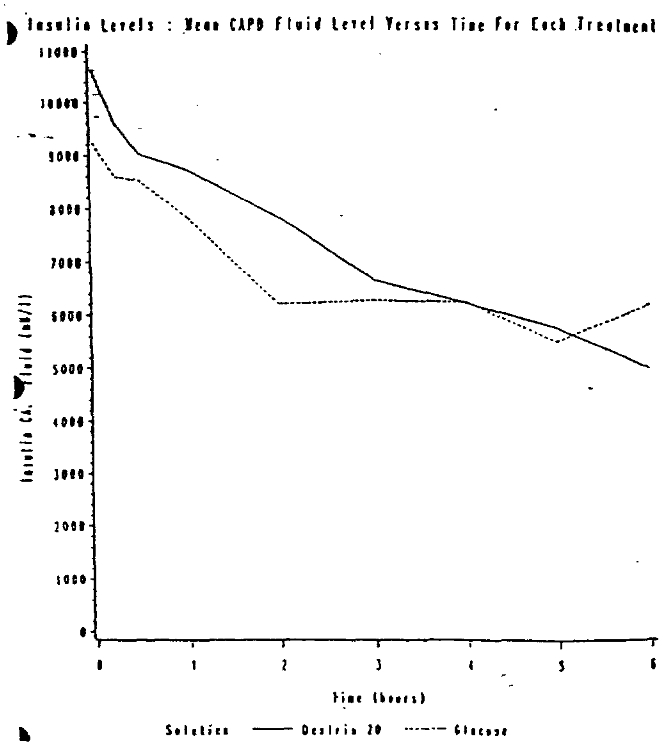

Figure 1. Mean CAPD fluid concentrations of insulin in both treatments.

Although the sample size was small, the sponsor concluded that insulin may be safely administered together with icodextrin, the same way that it is added to glucose CAPD fluid.

COMMENTS:

This study report did not include the assay description for insulin and glucose and quality control samples for the measurements.

Although the study showed that the difference in insulin plasma and dialysate levels in both treatment groups were not statistically significant, the study results cannot be evaluated properly.

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/s/

Elena Mishina
7/12/01 10:14:19 AM
BIOPHARMACEUTICS

Patrick Marroum
7/12/01 10:33:00 AM
BIOPHARMACEUTICS

MEMORANDUM

To: File, NDA 21-321

Through: Robert Temple, M.D., ODE I Office Director
Douglas Throckmorton, M.D., Division Director, DCRDP
Albert DeFelice, Ph.D., Supervisory Pharmacologist, DCRDP
James Willard, Ph.D., Pharmacology Reviewer, CDRDP
Russell Fortney, Project Manager, DCRDP

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

Subject: NDA 21-321 ; Extraneal, 7.5% Icodextrin w/v peritoneal dialysis solution
Tertiary Review of Pharmacology/Toxicology Data

Date: December 13, 2002

Dr James Willard conducted a review of the pharmacology and toxicology data which included 28-day intraperitoneal toxicity studies in rats and dogs, a standard genotoxicity battery, antigenicity testing in guinea pigs, and a combined intraperitoneal fertility and embryo-fetal toxicity study in rats. I presume this minimal toxicologic evaluation was accepted since the active ingredient, icodextrin, is a starch-derived glucose polymer obtained from corn.

The primary reviewer noted several problems with the design of the toxicity studies which confounded their interpretation. These included:

1) The use of the peritoneal dialysis (PD)-2 electrolyte solution at pH 5-6 as a control was not appropriate since it independently resulted in tissue pathology and appeared to be responsible for much of the toxicity observed with the icodextrin product. However, since the PD-2 electrolyte solution is the vehicle for the icodextrin peritoneal dialysis solution, the adverse events associated with this vehicle are clinically relevant.
   <u>**28-Day Rat Study**</u>: Renal tubular basophilia was observed in the PD-2 control and the 20% icodextrin groups, but not in the 5% glucose controls. Cardiomyopathy was observed in PD-2 controls (5 M/1F) and the 20% icodextrin group (2 M/ 3F), but not in the 5% glucose or 14% icodextrin groups. Glycogen deposits were noted in the livers of the 14% and 20% icodextrin groups.
   <u>**28-Day Dog Study:**</u> Decreased urinary excretion of sodium, increased urinary creatinine; Increased plasma glucose and alkaline phosphatase in 14% and 20% icodextrin groups. Serosal reactions in the peritoneum – equivocal reactions in 6/16 animals not treated with icodextrin (5% dextrose and PD-2 groups), moderate to strong reactions in all icodextrin treated animals (8/8 on 14%; 8/8 on 20% icodextrin).
   Dr Willard concluded that without appropriate controls or longer duration toxicity studies it is impossible to establish the safety of the 7.5% icodextrin dialysis solution.

2) Doses evaluated in the rat fertility/embryofetal toxicity study were quite low (less than human therapeutic exposures). The methods section of the reprotoxicity study states that 20 ml/kg/day of a 20% solution was selected as the maximum practical dose. In the general toxicity studies, doses of 30 ml/kg of 14% and 20% solutions were administered twice daily to increase exposures. Therefore, administration of higher doses is feasible. Dr Willard recommended that the fertility/embryo-fetal toxicity study be repeated with higher dose levels.

3) Dr Willard also recommended that toxicity studies of longer duration would permit further evaluation of peritoneal serosal reactions, and the liver, kidney, testicular, and cardiac effects such as cardiomyopathy and ECG changes.

Further discussions regarding the interpretation of the preclinical findings were held between Drs Lipicky, Stockbridge, DeFelice, and Willard and are documented in Dr DeFelice's memorandum to the file dated September 4, 2002. The conclusions are summarized below.
Drs Lipicky and Stockbridge concluded there was no evidence of ECG anomalies in icodextrin-treated animals relative to the 5% glucose controls.
Dr DeFelice felt there was no compelling or consistent evidence of target organ toxicity associated with icodextrin since similar toxicity profiles were observed with the PD-2 vehicle alone. He also states that it is his understanding that the clinical tolerability of the PD-glucose solution is well known. Extraneal has been approved in the United Kingdom since 1992, so I presume there are also long-term clinical safety data for the icodextrin PD solution.

I defer to the medical officers to determine whether there is adequate clinical safety data for the Extraneal icodextrin and low pH peritoneal dialysis solutions to waive the need for further toxicologic evaluations. However, I agree with Dr Willard that longer term toxicology studies with appropriate controls would most readily determine if there are chronic renal, liver, testicular, or cardiac adverse effects associated with low pH PD solutions alone or in combination with icodextrin. I also agree with Dr DeFelice's conclusion that repitition of the rat fertility/embryofetal toxicity study with higher doses is not warranted since the patient population would not be expected to parent children.

The preclinical sections of the labeling (p.8) are generally acceptable. I would suggest one small editorial change. Under **Carcinogenesis, Mutagenesis, Impairment of Fertility** , paragraph 2, first sentence...

A fertility study in rats where males and females were treated for four and two weeks, respectively, prior to mating and until day 17 of gestation at doses up to specifiy the high dose (1/3 the human exposure on a mg/m^2 basis) revealed low epididymal weights in parental males ...

FYI - The general convention is to state the doses studied and then provide the relative exposure data parenthetically.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

FROM: Albert DeFelice, Ph.D.: Supervisory Pharmacologist, HFD-110

TO: File, NDA 21-321

Re: Resolution of Remaining Pre-clinical issues

In his memorandum of 12/21/2001 to Drs. Lipicky and deFelice, Dr. Willard – the primary pharmacology/toxicology reviewer for the subject (Extraneal) NDA - identifies the status of four preclinical issues he raises in the memorandum of 11/15/2001:

I. Analysis of ECG from Extraneal-treated dogs.:
Drs Throckmorton, Stockbridge, Willard, and DeFelice re-visited initial ECG samples, and derived data, provided by Dr. Willard, all in the absence of any controls for pH and/or osmolality *per se*. It is my understanding that *the consensus of both medical officers was that there was no consistent or persuasive evidence of QTc prolongation relative to PD-glucose at the initial look* although all agreed that the study was not completely controlled. Additional EKGs have been submitted but without comprehensive analysis by the Sponsor. <u>Accordingly, as it now stands there is no firm or interpretable evidence of ECG anomaly relative to PD-glucose.</u>
II Dr. Willard recommends either adding the statement "

However, in my overview of the pre-clinical toxicity studies, I detected no compelling or consistent evidence of excess organ toxicity relative to PD-glucose to alert or project the need for chronic studies. It is my understanding that the clinical behavior and tolerability of the PD-glucose solution is well known.
III. Dr. Willard further recommends adding the following statement to the Labeling: '

However on November 26th an internal meeting was held between Dr. Douglas Throckmorton, Dr. Albert DeFelice, and Dr. Jim Willard to discuss this issue. It was decided that non-inferiority animal toxicology data was of insufficient quality and insufficient sample size to support the notion that extraneal provoked excess genital inflammation or decrease in uterine and ovarian weight vis a vis PD- Glucose. There for it was agreed to omit, from labeling,

IV. The fourth issue involved rash in patients. As Dr. Willard notes in the memo of 12/21/2001, that issue is adequately addressed in the current version of the labeling.
Recommendation: The current version of the Labeling adequately addresses the findings in the preclinical toxicology studies, recognizing the limitations on interpretability absent controls for pH and osmolality, and volume overload *per se*.

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/s/

Albert Defelice
9/4/02 03:39:34 PM
PHARMACOLOGIST

Nguyen, Quynh

From: CDER DocAdmin, DFS
Sent: Wednesday, September 04, 2002 3:44 PM
To: Nguyen, Quynh; Willard, James M; Throckmorton, Douglas C
Subject: DFS Email - N 021321 N 000 22-Dec-2000 - Memo to File

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Document room update the following:

	Decision Date	Decision Code
N 021321 N 000 22-Dec-2000	04-Sep-2002	NR:NO REPLY NECESSARY

Document Type: Memo to File
Submission Description: resolution of Pharm/tox issues.
PM activity: PM activity required

Author(s)/Discipline(s)

1. Albert Defelice, PHARMACOLOGIST

Signer(s)

1. Albert Defelice
   04-Sep-2002

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

From: James M. Willard, Ph.D., Pharmacologist, HFD-110

To: Albert Defelice, Ph.D., Pharmacology Team Leader, HFD-110
Raymond J. Lipicky, M.D. Director, Division of Cardio-Renal Drug Products

Subject: NDA 21-321 Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution

Date: 12/21/2001

This memo is to inform you of the resolution of the issues from the memorandum of 11/5/2001 of Extraneal labeling issues. The 11/5 memo is appended.

The first issue involves an analysis of ECG studies from Baxter Healthcare. This information has yet to be received.

The second issue involved either adding the statement

Dr. Temple stated there was no place to put the above statement in the labeling. The issue of a phase IV commitment for the recommended studies was not addressed.

The third issue involved adding the following statement to the labeling

A memo of 12/21/2001 dealt with that statement. No discussion took place on potential phase IV commitments to resolve the potential fertility issues.

The fourth issue involved rash in patients receiving Extraneal therapy. It was felt that with a few changes in the adverse event section that the rash issue was sufficiently covered.

This is my present understanding on where these issues presently stand.

Sincerely,

James M. Willard, Pharmacologist, DCRDP

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

From: James M. Willard, Ph.D., Pharmacologist, HFD-110

To: Albert Defelice, Ph.D., Pharmacology Team Leader, HFD-110
Raymond J. Lipicky, M.D. Director, Division of Cardio-Renal Drug Products

Subject: NDA 21-321 Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution

Date: 11/5/2001

In regard to labeling and recommended studies for NDA 21-321, Extraneal, I have the following comments.

The sponsor has still not finished an analysis of ECG tracings from 3 dog studies. The data was originally not analyzed sufficiently by the sponsor, despite the presence of irregularities, such as sinus arrhythmias and some evidence of QT prolongation and development of an irregular U wave. This analysis needs to be completed.

I recommended a 1-year dog toxicology study. 6 months would also be acceptable. The study should use an untreated group, an appropriate control group (i.e. lactated Ringer's, neutral pH), PD-2 electrolytes, 7.5 & 15% icodextrin in a neutral buffer as well as PD-2 electrolytes. I feel the longer-term study is needed to look at the changes in organs in a longer-term exposure, especially lungs, liver, kidneys and reproductive organs (would require ~28 dogs). In lieu of this study, perhaps adding to the labeling

I also recommended a rat fertility study be done. Part of that could be done in the above dog toxicology study, with sperm motility studies and checking organ weights in necropsy. The rat study should use a neutral pH control group, and should push the volume to see if that really does cause developmental problems in the embryos. It should also use exposures in excess of what would be anticipated in humans. In addition, a longer treatment period prior to mating would be appropriate, with 60 days being acceptable. A longer term, higher dose study is warranted in light of seeing some small changes in the low dose study that was done, and for the changes seen in the toxicology studies at higher doses. If these studies are not done, I would recommend strengthening the impairment of fertility section of the labeling to say

The only other issue I see in the labeling regards the appearance of a rash. Labeling should perhaps strengthen warnings to see your physician when a rash develops and should consider discontinuation of icodextrin therapy.

At present, these are my concerns with NDA 21-321.

Sincerely,

James M. Willard, Pharmacologist, DCRDP

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/s/

James Willard
1/2/02 08:35:38 AM
PHARMACOLOGIST

Albert Defelice
1/2/02 11:24:49 AM
PHARMACOLOGIST
I see no interpretable evidence of excess systemic or reproductive toxicity of icodextrinl/PD vs glucose/PD in the submitted studies that would justify Sponsor's committing to longer -term phase IV follow-up animal studies. I will write a memo.