CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Pharmacology Review(s)

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: 12/14/2001

Please refer to the draft labeling submitted to NDA 21-321 on 11/27/2001, document N-BZ. Following is a summary of 3 teleconferences with Baxter Healthcare Corporation as well as a summary of an internal meeting regarding this submission. Also included is a brief summary of issues arising from the pharmacological/toxicological studies submitted.

The basis for many of the peritoneal dialysis products presently on the market is that they use a buffer similar to the PD-2 electrolyte solution. The PD-2 electrolyte solution is composed of 5.4 g sodium chloride, 4.5 g sodium lactate, 257 mg calcium chloride and 51 mg magnesium chloride. In the past, the FDA position has been that the solution is a physiological saline and therefore is of no pharmacological concern. This is in part due to 1) peritoneal dialysis came into common use around 1962, prior to many present FDA regulations, and 2) the first NDA approved for peritoneal dialysis, 17-512, was not a submission of peritoneal dialysis as a treatment, but of the switch from glass to plastic containers. In NDA 17-512 the overriding concern was more the potential carcinogenicity of plasticizer residues. The PD-2 electrolyte solution, however, is at pH 5.0 in order to reduce the level of glucose degradation products generated by the heat sterilization procedure.

The decision as to what the control group for the toxicological studies of NDA 21-321 was confounded by the study design utilized by the sponsor. Absent the use of control groups for treatment, pH, and volume, the basic choice of control group was between the PD-2 electrolyte solution and 5% Glucose in PD-2 electrolyte solution. In the animal studies, there were significant pathological signs in the toxicological studies of the PD-2 electrolyte solution, especially to organ systems involved in dealing with acidification, namely the kidneys and lungs. Interestingly, the 5% glucose in PD-2 electrolytes showed generally the fewest pathological signs, probably indicative of some mechanism involving sodium-proton and sodium-glucose exchange systems probably reducing toxicity. Icodextrin-treated animals were generally closer to the PD-2 electrolyte solution for pathological signs. The results were further confounded by veterinary therapeutic intervention to the icodextrin-treated dogs, potentially ameliorating the toxic effects.

The studies submitted by Baxter Healthcare to support approval for Extraneal PD solution generally utilized the PD-2 electrolyte solution as a control, with the 5% glucose in PD-2 electrolytes as a comparator product. Although this was reasonable in light of the FDA's position on the PD-2 electrolytes, this has created a difficulty in data interpretation, since the control is frequently the most toxic treatment modality. An appropriately controlled study, with an untreated animal group as well as appropriate controls for volume, pH, and osmolarity should have been included and would have greatly aided data interpretation. At present, there are few alternatives to the PD-2 electrolytes in peritoneal dialysis solutions, although several alternatives are in development. I would like to recommend that future dialysis solutions be compared to the PD-2 electrolytes, and if they prove to be less toxic, that the PD-2 based solutions be reconsidered in light of results demonstrating the toxicity of this solution.

As a result of this difficulty in data interpretation due to study design, the following statement that was going to be added to the labeling of the Extraneal labeling in the Carcinogenesis, Mutagenesis and Impairment of Fertility section, will not be included:

Sincerely,

James M. Willard
Pharmacologist, DCRDP

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Willard
12/21/01 11:22:49 AM
PHARMACOLOGIST

Albert Defelice
12/21/01 11:55:49 AM
PHARMACOLOGIST

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
Douglas Throckmorton, M.D. Deputy Director, Division of Cardio-Renal Drug Products
Raymond J. Lipicky, M.D. Director, Division of Cardio-Renal Drug Products

Subject: NDA 21-321 Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution, minutes from a telecon on 11/19/2001

Date: 11/28/2001

On Monday, November 19, 2001, Ms. Mary Kay Rybicki, Associate Director for Regulatory Affairs at Baxter Healthcare called to discuss labeling issues on Extraneal, specifically, the statement that:

[redacted] The teleconference was attended by James M. Willard of the FDA, and by Mary Kay Rybicki of Baxter. The conversation basically concluded a discussion of the data submitted by Baxter and analyzed by Dr. [redacted] that basically the nature of the data was such that it was difficult to reach any firm conclusions on whether edema or inflammation was occurring in the animal populations.

Sincerely,

James M. Willard, Pharmacologist, DCRDP

APPEARS THIS WAY
ON ORIGINAL

Memorandum

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Raymond J. Lipicky, M.D. Director, Division of Cardio-Renal Drug Products

Subject: NDA 21-321 Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution, minutes from an internal meeting on 11/26/2001

On Monday, November 26th, an internal meeting was held between Dr. Douglas Throckmorton, Deputy Director, DCRDP, Dr. Albert Defelice, Supervisory Pharmacologist, and Dr. James Willard, Pharmacologist; to discuss the Baxter labeling. It was decided that the data submitted, being from a non-inferiority type of study, was of insufficient quality and insufficient sample size and would not support that extraneal was potentially causing more of the observed genital inflammation, or the decrease in ovarian or uterine organ weights than the comparator product, 5% glucose in PD-2 electrolytes. Therefore, it was decided to omit the following statement from the extraneal label [redacted]

Sincerely,

James M. Willard, Pharmacologist, DCRDP

Memorandum

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

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

To: Quynh Nguyen, Regulatory Health Project Manager, HFD-110
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, minutes from a telecon on 11/15/2001

Date: 11/19/2001

On Thursday, November 15, 2001, Ms. Mary Kay Rybicki, Associate Director for Regulatory Affairs at Baxter Healthcare called to arrange a teleconference to discuss labeling issues on Extraneal, specifically, the statement that:

[redacted]." The teleconference was arranged for 12:30pm EST, and was attended by James M. Willard of the FDA, and by Mary Kay Rybicki, Randy White, Leo Martis, and [redacted] (veterinary pathologist) of Baxter. I had previously stated that, and that testicular atrophy, although it did occur, was not the issue, but testicular inflammation, being a more common problem in dogs and rats was an issue, and that [redacted] should be replaced with [redacted] in the labeling. It was also communicated to Baxter that after discussions with Dr. Defelice, although there was a decline in ovarian and uterine organ weights compared to normal, untreated animals, since the drop was also present in the 5% Glucose treated group we would be willing to remove that from the labeling. Dr. [redacted] from Baxter claimed that quadrupeds were more likely than bipeds to develop testicular effects in peritoneal dialysis. Baxter asked if they could have Dr. [redacted] a veterinary pathologist could evaluate the data and data from some other peritoneal dialysis buffers, and e-mail the report on Monday, November 19, 2001. That was fine, with a follow-up telecon to occur after the data and report were evaluated.

Sincerely,

James M. Willard, Pharmacologist, DCRDP

Memorandum

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To: Quynh Nguyen, Regulatory Health Project Manager, HFD-110
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, minutes from a telecon on 11/13/2001

Date: 11/13/2001

On Tuesday, November 13, 2001, Ms. Mary Kay Rybicki, Associate Director for Regulatory Affairs at Baxter Healthcare called to arrange a teleconference to discuss labeling issues on Extraneal, specifically, the statement that: [redacted] The teleconference was arranged for 1pm EST, and was attended by James M. Willard of the FDA, and by Mary Kay Rybicki, Randy White, Leo Martis, and Jill Glossin of Baxter. I pointed out that I had been mistaken on one point, and that testicular atrophy, although it did occur, was not the issue. but testicular inflammation, being a more common problem in dogs and rats was an issue, and that [redacted] should be replaced with [redacted] It was also pointed out that there are problems of interpretation of the data as appropriate control groups were not used in the study. Discussion centered on data interpretation, with the representatives of Baxter claiming that since the treated groups were no worse than the control, there were no treatment-related effects. It was pointed out to them that the control group results were abnormal, and that the control buffer was part of the drug product, and was given to patients. Therefore, adverse effects attributed to the buffer, and echoed in the drug product, could not just be dismissed, but had to be considered. Baxter asked if they could have a veterinary pathologist evaluate the data and hold further discussions on Thursday, November 15, 2001. It was decided to hold a further teleconference on Thursday, November 15, 2001.

Sincerely,

James M. Willard, Pharmacologist, DCRDP

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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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

Memorandum

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Date: 11/5/2001

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

Sincerely,

James M. Willard, Pharmacologist, DCRDP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Willard
11/8/01 05:26:09 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-321
Review number: Z
Serial number/date/type of submission: 000/12/22/2000/NDA
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Baxter Healthcare Corporation
Manufacturer for drug substance : Baxter

Reviewer name: James M. Willard, Ph.D., Pharmacologist
Division name: Division of Cardio-Renal Drug Products
HFD #: 110
Review completion date:

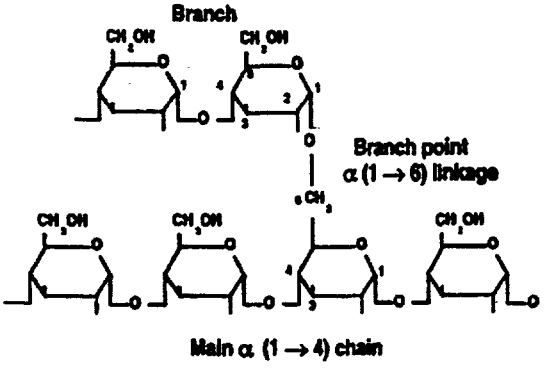
Drug:

Trade name: Extraneal 7.5% w/v PD solution
Generic name (list alphabetically): Icodextrin
Code name:
Chemical name: Icodextrin
CAS registry number: 9004-53-9

Mole file number:

Molecular formula/molecular weight: EXTRANEAL (7.5% Icodextrin) Peritoneal Dialysis Solution is a peritoneal dialysis solution containing the colloid osmotic agent icodextrin. Icodextrin is a starch derived, water soluble glucose polymer linked by alpha (1-4) and alpha (1-6) glucosidic bonds with a weight average molecular weight between [redacted] and a number average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of icodextrin is:

Structure:



Relevant INDs/NDAs/DMFs: [redacted], DMF [redacted] DMF [redacted] DMF [redacted]

Drug class: osmotic agent

Indication: Treatment of Chronic Renal Failure

Clinical formulation:

Icodextrin	**g**
Sodium Chloride	**g**
Sodium Lactate	**g**
Calcium Chloride	**mg**
Magnesium Chloride	**mg**

Route of administration: Intraperitoneally via catheter

Proposed use: Continuous Ambulatory Peritoneal Dialysis

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Icodextrin is a long chain glucose polymer that has been isolated by partial digestion of maltodextrin obtained from corn. The usage proposed here is as an osmotic agent in peritoneal dialysis. Generally a glucose solution is utilized for this purpose, however, many of the patients with end stage renal disease (ESRD) are diabetic. Icodextrin has been proposed as an alternative to glucose for this purpose and because peritoneal ultrafiltration may be prolonged in the long dwell times of 8-12 hours. At present, the usage of icodextrin 7.5% solution proposed in NDA 21-321 is limited to one long dwell time (8-12 hrs), and not for continuous usage.

Safety evaluation: Evaluation of the safety of icodextrin in the context of this study was difficult. Unfortunately, many of the non-clinical safety studies were carried out with a PD-2 electrolyte solution at a pH of 5.0 to 6.0 as the control. In the animal studies, the electrolyte solution by itself demonstrated electrolytic alterations in the serum and urine of animals along with apparent signs of nephrotoxicity in dogs and rats and potential signs of hepatotoxicity. Additionally, the longest toxicology studies were only of 28 days duration. This made it more difficult to interpret damage found upon necropsy and histopathology of the animals. The addition of glucose and to some lesser extent, icodextrin, to the PD-2 electrolyte solution did seem to lessen some of the toxicity of the PD-2 electrolyte solution, however, with the results presented here, it is difficult to determine that result. Although in general it would be anticipated that icodextrin is fairly non-toxic, the inappropriate choice of controls and the shortness of the toxicology trials makes it difficult to reach any valid assessment of the safety of icodextrin 7.5% solution. In addition, serosal reactions in icodextrin exposed tissues and ECG alterations related to icodextrin exposure were seen. Other findings were of alterations to serum and urine electrolytes and volume, significant changes that indicate potential problems. Further studies are needed.

The situation has arisen as to what is a good control to use for these non-clinical Pharm/tox studies. Virtually all of the experiments have used the PD-2 electrolyte solution at pH 5.0-6.0 as a control. The toxicology studies reviewed here demonstrate that this is not a typical control solution, and leads to development of various pathologies in the rat and dog. In one sense it is a good choice, it is the solution that the icodextrin will be presented to the patient dissolved in, and similarly to the glucose solutions tested. However, when the PD-2 electrolytes are looked at compared to normal, untreated animals, it is obvious that the solution causes the emergence of various pathologies in the animals. Generally, the choice of a carrier agent in pharmaceuticals, one looks for a neutral or supportive media, not a damaging one unless there is none other available. Some comparisons were done with normal saline (0.9% NaCl), this is also inadequate, as it is not a balanced electrolyte solution, and effects other electrolytes in the body. The PD-2 electrolyte solution is basically a lactated Ringer's solution that has been acidified. Therefore, a neutrally buffered lactated Ringer's may be a good control system to use. However, I would also recommend either an untreated control group, or a submission including the recent historical average values for that species in the lab performing the studies. Presently, there is a sizable research effort into neutral pH peritoneal dialysis solutions. If the sponsor has a solution that is known to have little effect on the basic physiology of the test animals, that may be a more appropriate control, but this should not be done without prior consulatation with the FDA.

Another serious consideration is the dosing protocols. This is especially important in light of the way these solutions are utilized in humans, and the potential toxicity of the PD-2 electrolyte solution by itself. For example, in the dog and rat 28 day toxicity studies, the animals received 30 ml/kg of solution b.i.d. For the 14 and 20 % icodextrin groups, this correlates to a dose of 8.4 and 12 g/kg/day, respectively. For the human dosage, 3 to 5 exchanges per day of a 7.5 % solution corresponds to an exposure level of 6.75 to 11.25 g/kg/day, respectively. Therefore, the 28 day studies did not give higher exposures to the icodextrin, and actually reduced exposure to the PD-2 electrolytes, as compared to the human exposures anticipated if icodextrin were the sole agent used for peritoneal dialysis. For one exchange per day of icodextrin, the human exposure is reduced to 2.25 g/kg. Since the rat and dog studies did see various toxic pathologies emerging, these results would not support allowing the sponsor to increase patient exposure without further studies.

Safety issues relevant to clinical use: Although the icodextrin 7.5% formulation is intended for a patient base that is suffering from End Stage Renal Disease, generally patients are diagnosed when 75% of the kidney has malfunctioned. Since there is 25% residual kidney function, it would seem best to preserve as much function as possible. If the icodextrin solution, in conjunction with the PD-2 acidic electrolyte solution speeds the total time to failure of the kidneys, it may be worth examining further. Additionally, if the icodextrin solution leads to increased deposition of glycogen in the liver and to liver damage, this may be worth examining. Liver problems are frequently comorbid with ESRD.

There appear to be gender specific issues in the dog and rat in their reaction to icodextrin.

Part of the justification of the development of the icodextrin osmotic agent was to benefit diabetics by using a less bio-available glucose polymer. Unfortunately, in the studies here, in dogs the icodextrin treated animals reached higher serum glucose values over a prolonged period of time, even above that of the glucose solutions alone.

Additionally, in clinical usage in the United Kingdom, reports have been growing of allergic responses developing to icodextrin leading to discontinuation of the treatment. The submission does provide data from three studies looking at anaphylaxis in guinea pigs, all of which were negative. A better model system would have been the rat paw edema model, which is frequently used for studies of dextran allergies. The use of this system would also allow the sponsor to determine if the hapten therapy used for dextran allergies would be useful in helping the patients to continue using icodextrin for peritoneal dialysis and perhaps extend the therapy. In support of the allergy potential of the icodextrin solutions, all the dogs receiving icodextrin exhibited serosal reactions in tissues exposed to icodextrin. Many of these reactions were rated a 3+, whereas in the glucose or solution alone groups there were few reactions and most were rated +/-. Therefore allergic reactions may be a serious issue icodextrin therapy. The dog model would potentially be a good model system to examine hapten or other therapies with the idea of prolonging icodextrin therapy.

Other clinically relevant issues: Testicular atrophy and inflammation were common problems in the rat population. In the dogs, many had immature testicular development, an unusual finding in a population of 6-6.5 month dogs weighing 10kg. In the rat fertility studies, low dosages, lower than those used in the toxicity testing, and most of them lower than the proposed human doses were used.

And the pregnant females did not receive the highest dose in the study. Therefore, it is still not determined if icodextrin 7.5% solution may effect fertility or reproduction. As with many of the other studies, the use of the electrolyte solution, which also caused potential problems with the testes, muddles the issue of the safety of the drug product.

The sponsor, along with other companies and researchers are working on new, neutral pH dialysis solutions that may resolve many of the issues found here, the sponsor should be encouraged to continue these efforts.

Conclusions: In drug evaluation, the entire drug product must be evaluated. In this drug submission, the PD-2 acidic electrolyte solution, which is presently used in peritoneal dialysis, was found to potentially be nephrotoxic, may have male fertility effects, and possible hepatotoxicity. Unfortunately, the studies all show some level of damage in studies utilizing the PD-2 electrolytes. Although kidney failure in the test animals may make for a better test of the icodextrin 7.5% solution for dialysis, it does not help to demonstrate the safety of the icodextrin 7.5% solution for dialysis.

Although icodextrin itself may be an innocuous compound, in the studies presented here, it is difficult to point to any demonstration of safety. Many of the studies were done with low doses, and many of the studies used inappropriate controls to demonstrate the safety of icodextrin 7.5% solution for dialysis. Without longer term toxicity studies to determine the progression of the kidney and liver injury seen in the various studies, along with the absence of a good study using an appropriate control, it is not possible to determine from the results here the safety of icodextrin 7.5% solution for dialysis. The only conclusion is that the icodextrin 7.5% solution for dialysis is not acutely toxic. However, directly related to icodextrin therapy in these model systems are the allergenic serosal reactions found in the dogs, and the

Communication review:

Labeling review: The labeling for this drug should state:

RECOMMENDATIONS: Icodextrin 7.5% solution for dialysis is presently in use in the United Kingdom. Under appropriate physician monitoring, patients with End Stage Renal Disease should be able to tolerate therapy with icodextrin 7.5% solution for dialysis for the long dwell periods without great difficulty. The PD-2 electrolytes are presently in use due to the sterilization procedure adopted (glucose breaks down in high heat and pressure at neutral pH) for the glucose containing peritoneal dialysis fluids. However, further study is needed of the peritoneal serosal reactions from animals receiving icodextrin, studies of bicarbonate levels and lactate are needed to further understand acid/base relations, cardiac effects as seen in the occurrence of cardiomyopathies and ECG changes should be further studied, expecially since this patient population is very susceptible to cardiac events.

Longer toxicology studies should be performed to determine whether the kidney and hepatic toxicities seen here resolve or further develop into serious problems. Comorbidity of hepatic complications is frequent with ESRD patients.

The issue of what an appropriate control is, is key to these studies. The PD-2 electrolyte solution as constituted here is not appropriate since it is probably the most toxic treatment used. A puportedly inactive control that causes more pathology than any of the drug treatments tested is obviously not appropriate. In some cases the 5% glucose/PD-2 solutions could be used for comparisons. However, with regard to effects on the study animals, the glucose solution was less damaging to the animals than the icodextrin solutions, which in turn were less toxic than the electrolyte solution alone. There are at present some neutral pH solutions being developed for peritoneal dialysis, but at this time, none are in general usage. If the studies provided clinical norms for the various parameters studied as typically seen in that species, and utilized a neutral pH lactated Ringer's solution for the control and for comparison with the electrolyte solution, that may be the best alternative at this point in time. Some small, preliminary studies should probably be done with an assessment of suitability before launching a large study. These studies should be done in consultation with the FDA.

Internal comments: I would like to see a higher dose fertility study, and longer toxicity testing done to study the liver and kidney effects, perhaps as part of a post-marketing commitment. Cardiac studies.

External recommendations (to sponsor):

Draft letter content for sponsor (if not same as above):

Future development or issues: Development of neutral pH peritoneal dialysis solutions, and use of appropriate controls in the future would speed the process of evaluating future formulations. Fertility studies performed at higher doses than the human dose equivalent should be done. Longer toxicity studies should be done to further understand the kidney and liver damage.

Reviewer signature: /S/

Team leader signature [concurrence/non-concurrence]:

cc: list:

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

Studies reviewed within this submission:

5.1-1 Comprehensive Table of Nonclinical Pharmacology and Toxicology Studies

Study Type	Study Title	Test Article	Laboratory
PHARMACOLOGY STUDIES			
Pharmacology Non-GLP	Dextrin 20 Effects on the Respiratory and Cardiovascular Systems of the Anesthetized Rabbit. **Report No. 239084**	2.5, 5, 10% Dextrin 20 in saline.	
Pharmacology Non-GLP	Dextrin 20 Effects on the Gastrointestinal Tract. **Report No. 239117**	0.25, 0.5, 1.0% Dextrin 20 in saline.	
Pharmacology Non-GLP	Dextrin 20 Effects on Smooth Muscle. **Report No. 239095.**	2.5, 0.5, 10, 25% Dextrin 20 in Jalon/Tyrode solution.	
Pharmacology Non-GLP	General Pharmacology Study of Icodextrin. **Report No. 7L828**	7.5, 25% Icodextrin in electrolyte solution.	
Pharmacology Non-GLP	Effects of Intraperitoneal Administration of Icodextrin on the Circulating Blood Volume and Blood Electrolytes in Rats **Report No. 97-I-688**	7.5, 25% Icodextrin in electrolyte solution.	
ACUTE TOXICITY STUDIES			
Acute Toxicity (mouse) GLP	Electrolyte Solution with 20% Dextrin: Acute Intravenous Toxicity (limit) Test in Mice. **Report No. 6464**	20% Dextrin 20 in electrolyte solution.	
Acute Toxicity (mouse) GLP	Electrolyte Solution with 20% Dextrin: Acute Intraperitoneal Toxicity (limit) Test in Mice. **Report No. 6466**	20% Dextrin 20 in electrolyte solution.	
Acute Toxicity (rat) GLP	Electrolyte Solution with 20% Dextrin: Acute Intravenous Toxicity (limit) Test in Rats. **Report No. 6463**	20% Dextrin 20 in electrolyte solution.	
Acute Toxicity (rat) GLP	Electrolyte Solution with 20% Dextrin: Acute Intraperitoneal Toxicity (limit) Test in Rats. **Report No. 6465**	20% Dextrin 20 in electrolyte solution.	
Acute Toxicity (rat) GLP	The Single Dose Toxicity Test of Icodextrin by Intraperitoneal Administration in Rats. **Report No. 9-292**	7.5, 13.5, 25.0% Icodextrin in electrolyte solution.	
Acute Toxicity (rat) GLP	The Single Dose Toxicity Test of Icodextrin in Rats by Intraperitoneal Administration at a Large Volume. **Report No. 9-314**	7.5% Icodextrin in electrolyte solution.	
Acute Toxicity (Dog) Non-GLP	The Single Dose Toxicity Test of Icodextrin by Intraperitoneal Administration in Beagle Dogs. **Report No. 9-260**	7.5, 13.5, 25% Icodextrin in electrolyte solution.	
MULTIPLE DOSE TOXICITY STUDIES			
Multi-Dose Toxicity (Rat) GLP	Dextrin Polymer 7 Day Peritoneal Fluid Exchange Feasibility Study in Rats. **Report No. 7390**	14, 20% Dextrin Polymer in electrolyte solution.	
Multi-Dose Toxicity (Rat) GLP	Dextrin Polymer Peritoneal Fluid Exchange Pilot Feasibility Study in Rats. **Report No. 7400**	20% Dextrin Polymer in electrolyte solution.	
Multi-Dose Toxicity (Rat) GLP	Dextrin Polymer 28 Day Peritoneal Toxicity Study in Rats. **Report No. 7423**	14, 20% Dextrin Polymer in electrolyte solution.	
Multi-Dose Toxicity (Dog) GLP	Dextrin Polymer 7 Day Intravenous Toxicity Study in Dogs. **Report No. 5062**	2.5, 10, 20% Dextrin Polymer in saline.	

5.1-1 Comprehensive Table of Nonclinical Study Reports for Icodextrin – Cont.

Study Type	Study Title	Test Article	Laboratory
MULTIPLE DOSE TOXICITY STUDIES – Continued			
Multi-Dose Toxicity (Dog) GLP	Dextrin Polymer Peritoneal Fluid Exchange Pilot Feasibility Study in the Beagle Dog. **Report No. 7672**	14, 20% Dextrin Polymer in electrolyte solution.	
Multi-Dose Toxicity (Dog) GLP	Dextrin Polymer 28 Day Peritoneal Toxicity Study in Dogs. **Report No. 7523**	14, 20% Dextrin Polymer in electrolyte solution.	
SPECIAL TOXICITY STUDIES			
Antigenicity Study (Guinea Pig) GLP	Evaluation of Potential for Icodextrin to Induce Anaphylaxis in Guinea Pigs. **Report No. 10652**	7.5% icodextrin in electrolyte solution.	BAX
Antigenicity Study (Guinea Pig) GLP	Antigenicity Study of Icodextrin. **Report No. 8L199**	7.5% Icodextrin in electrolyte solution.	
PMN Chemotaxis *(In vitro)* GLP	Effects of Icodextrin on chemotaxis of Human Leukocytes. **Report No. 97-I-689**	7.5, 15, 25% Icodextrin in electrolyte solution.	
MUTAGENICITY STUDIES			
Genetic Toxicity (Ames Test) GLP	Dextrin 20 Powder, Batch No. QC001/B: Testing for Mutagenic Activity with *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100. **Report No. 6814**	Dextrin 20 in water.	
Genetic Toxicity (CHO Cells) GLP	Dextrin 20 Powder: Chromosomal Aberrations Assay with Chinese Hamster Ovary Cells*in vitro*. **Report No. 8263**	Dextrin 20 in cell culture media.	
Genetic Toxicity (mouse) GLP	Dextrin 20 Powder: Micronucleus test in bone marrow of CD-1 mice. **Report No. 8468**	20% Dextrin 20 in water.	
REPRODUCTIVE TOXICITY			
Reproductive Toxicity (rat) GLP	Icodextrin Combined Study of Effects on Fertility and Embryo-Fetal Toxicity in CD Rats by Intraperitoneal Administration. **Report No. 99 4906**	20% Icodextrin in electrolyte solution.	
PHARMACOKINETIC AND METABOLISM STUDIES			
Distribution (Anephric Rat) non-GLP	Preliminary Study for Distribution Study of Icodextrin in Rats. **Report No. 10-1124**	15% Icodextrin in electrolyte solution.	
Distribution (Anephric Rat) non-GLP	Distribution Study of Icodextrin in Rats. **Report No. 10-890**	15% Icodextrin in electrolyte solution.	
Pharmacokinetic (Rat)	Report on the Pharmacokinetic Studies of Dextrin 20 in the Rat. **Report No. PK-RAT (Substudy of Report 7423)**	14, 20% Dextrin 20 in electrolyte solution.	ML
Pharmacokinetic (Dog)	Report on the Pharmacokinetic Studies of Dextrin 20 in the Dog. **Report No. PK-DOG (Substudy of Report 7523)**	14, 20% Dextrin 20 in electrolyte solution.	ML

Studies <u>not</u> reviewed within this submission:

Introduction and drug history: Peritoneal dialysis is a method of treatment for kidney failure primarily in end stage renal disease. The signs of kidney disease often do not appear early since the kidneys have a large capacity and until approximately 75% of the kidneys function is lost few signs of pathology appear in various clinical tests. In general, peritoneal dialysis uses a hyperosmolar solution that draws fluid and toxins and waste products from the body, using the peritoneal membrane as a filtering system. Two major modalities of peritoneal dialysis are presently employed, Continuous Ambulatory Peritoneal Dialysis (CAPD) and Continuous Cycling Peritoneal Dialysis (CCPD). In this context, continuous refers to the patient always having dialysis fluid in the peritoneum leading to continuous filtration through the peritoneal membrane. Many of the early methods involved intermittent exchanges carried out in a hospital setting. CAPD is considered ambulatory because except when the patient is exchanging the fluid, they are ambulatory. The large fluid volume (approximately 2 L for a 70 kg individual) acts in concert with the peritoneal membrane to filter the blood and act as a replacement kidney. Generally patients on CAPD do 3 to 5 exchanges per day. CCPD, or as it is sometimes known Automated Peritoneal Dialysis (APD) uses a machine called a cycler. While the patient is sleeping, the cycler does from 3 to 5 exchanges. Then, during the day, the patient leaves the fluid in the peritoneum, this longer period is called the dwell.

Icodextrin 7.5% solution in PD-2 electrolytes is a formulation presented here for use in patients on CAPD for the long dwell period. This could be either a long period during the daytime (i.e. working hours), or overnight while the patient is sleeping, depending on lifestyle and access to exchanging the dialysis solution. Icodextrin has been proposed to replace the 1.5, 2.25 and 3.5 % glucose solutions presently used in dialysis for the long dwell period. Icodextrin is a glucose polymer derived from maltodextrin, a product of corn starch. Icodextrin is thought to be primarily a polymer with 1,4 glucosidic linkages, and probably some remaining 1,6 glucosidic linkages making branching off the linear 1,4 glucosidic polymer. Structurally, this is identical to glycogen, the common glucose storage system in the body. Serum amylases and glycosidases readily breakdown glycogen to glucose, and similarly act on icodextrin.

The use of icodextrin in peritoneal dialysis has been proposed to increase the length of ultrafiltration during dwell times. Glucose, when used in peritoneal dialysis, is a small molecule that is able to cross the peritoneal membrane into the blood stream. Once glucose levels are sufficiently reduced in the peritoneum, ultrafiltration and the removal of wastes from the blood stream declines and may even reverse. Icodextrin, being a glucose polymer, is postulated to not cross the peritoneal membrane until it is sufficiently broken down by enzymes. However, some of the glucose and larger molecule removal from the peritoneum occurs through the mesenteric lymph nodes, which is not so dependent on the breakdown of icodextrin.

In drug evaluation, the entire drug product must be evaluated. In a brief search of FDA documents, in the past, the glucose-based peritoneal dialysis solutions received very little review since all the ingredients are considered safe individually, and there was no reason to consider them unsafe in combination. However, one problem that was overlooked was that the PD-2 electrolyte solution in the approved peritoneal dialysis solutions is at a pH of 4.9 to 6.0, very acidic. Considering the large volume of solution is given to the patient, equal to approximately 40-50% of the circulating blood volume, and that the acidic solution is renewed at regular intervals, the consequences of potential metabolic acidosis should be considered. The rationale used for maintaining an acidic solution is the reduction of the breakdown of glucose in the process of heat-sterilization of the peritoneal dialysis

solutions. Patients generally begin peritoneal dialysis with 25% kidney functionality. The preservation of that function while supplementing the kidneys' function should be a priority of dialysis.

Icodextrin for peritoneal dialysis was approved for marketing in the United Kingdom in 1992 by ML Laboratories as Icodial, and in 1997 was approved and marketed by Baxter Laboratories in an agreement with ML Laboratories. Icodextrin solutions have also been approved in the United Kingdom for prevention of abdominal adhesions following surgery.

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS

PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action: Icodextrin is a colloidal osmotic agent for use in peritoneal dialysis

Drug activity related to proposed indication: osmotic agent

Secondary pharmacodynamics: breakdown to glucose monomers to pentamers

Pharmacology summary:

Pharmacology conclusions:

SAFETY PHARMACOLOGY:

Neurological effects: Not done

Cardiovascular effects:

Study title: Effects on the Respiratory and Cardiovascular Systems of the Anaesthetized Rabbit

Key study findings:

Study no: 239084
Volume #, and page #: Vol. 1.7, pages 93-154
Conducting laboratory and location: [redacted]

Date of study initiation: 11/20/1990
GLP compliance:
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Dextrin 20, Batch # QC001/B, 92.5-98.1% purity
Formulation/vehicle: 0, 2.5, 5, or 10% dextrin 20 in 0.9% sterile saline

Dosing:

Species/strain: New Zealand White Rabbit
#/sex/group or time point (main study): 2 males
Age: 15-17 weeks
Weight: 2.595 – 2.713 kg
Doses in administered units: ml/kg

Route, form, volume, and infusion rate: Intravenous, 1 ml/kg

Study Number 239084: vol 1.7 p. 93-154
Only a small, transient effect on heart rate was seen. However, see the study in General Pharmacology.

Study Number 239084: vol 1.7 p. 93-154

EFFECTS ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS OF THE ANAESTHETIZED RABBIT

By: [redacted]

2 New Zealand White Rabbits (male; weighing 2.5 or 2.7 kg; 15 weeks old) were anaesthetized with urethane (1.5g/kg in 0.9% sterile saline).

Upon the induction of anaesthesia the trachea was intubated, and a cannula (containing 2 µg Heparin /ml) was inserted into the left arteria carotis and linked up with a pressure transducer [redacted] A second cannula (containing physiological saline) was inserted into the marginal ear vein.

The sternum was connected to a force—displacement transducer [redacted] by a silk thread in order to measure the respiration rate.

Both transducers were connected to a Grass Polygraph paper recorder type [redacted]

Heart rate was recorded by means of a direct writeout using a Grass plug—in ECG [redacted], connected to the output from a Grass Blood Pressure Preamplifier.

TREATMENT WITH TEST OR CONTROL ARTICLES

Method: Intravenous, into the marginal ear vein, by slow injection.

Dose levels: The animals received successive application of control(0%) or test article solution at concentrations of 2.5, 5 and 10%. The time interval between each application was approximately 20 minutes, unless significant effects were observed when the next dose was administered upon recovery. Immediately after each injection, an equivalent volume (1 ml/animal) of vehicle was administered via the same catheter to wash out the residual test solution.

TREATMENT WITH NORADRENALINE

Method: Intravenous, into the marginal ear vein.

Dose level: 2.5 µg/kg body weight.

Dose level rationale: Previously used in studies of this type.

Dose volume: 0.1 ml/kg body weight. A sufficient volume of vehicle was administered via the same catheter to wash out the residual standard solution.

Frequency of application: Once, 10 minutes after each application

Mci-adrenaline source: [redacted]

Vehicle: Saline (0.9% [redacted]), sterile.

Vehicle source: [redacted]

OBSERVATIONS

Blood pressure: Continuously up to the end of the experiment

Heart rate: Continuously up to the end of the experiment

Respiratory rate: Continuously up to the end of the experiment

Recording time:Up to 30 minutes after the last dose.

Animals were only treated when a stable blood pressure trace was recorded.

Results: Icodextrin administration resulted in a transient increase in Heart Rate and Blood Pressure. The increase was small, up to 16%, and generally values returned to baseline after 5 minutes post-dosing.

Comments: Only a small, transient influence of icodextrin on cardiac, none on respiratory rates, in this small sample of 2 rabbits. However, this study was not done with the PD2 electrolyte system at pH 5-6

Pulmonary effects: Study Number 239084: vol 1.7 p. 93-154
No Effect was seen. See above review of Respiratory and Cardiovascular studies.

Renal effects: See the General Pharmacology Study in the other category.

Gastrointestinal effects:

Project 239117: Effects on the Gastrointestinal Tract vol. 1.7, p. 155-191
No effects were seen in this study.

PROJECT 239117: EFFECTS ON THE GASTROINTESTINAL TRACT VOL. 1.7, P. 155-191

The aim of this study for the sponsor was "to assess the effect of Dextrin 20 solution administered by the intraperitoneal route on intestinal *peristaltis**". The following information from the sponsor outlines the study setup.

APPEARS THIS WAY
ON ORIGINAL

PROJECT 239117
DEXTRIN 20

EFFECT ON GASTROINTESTINAL TRACT

Intestinal Motility - Charcoal Propulsion in Mice

TEST AIM	To examine possible inhibitive or stimulating effects of the test substance on gastrointestinal peristalsis.
TEST SYSTEM	
Test Species	NMRI Mouse, outbred, SPF Quality
Rationale	Commonly used test species for studies of this type
Source	
Number of animals/group	5 males
Total number of animals	25 males
Age (at treatment)	5 weeks
Body weight range (at treatment)	22 - 29 grams
Identification	Fur color-codes with an indelible felt-tip pen
Randomization	Randomly selected at time of delivery
Acclimatization	7 days, after veterinary examination

PROJECT 239117
DEXTRIN 20

ALLOCATION

% solution	Group 1 Control Vehicle	Group 2 Dextrin 20 0.25 %	Group 3 Dextrin 20 0.5 %	Group 4 Dextrin 20 1 %	Group 5* Reference substance
Animal Number	1 - 5	6 - 10	11 - 15	16 - 20	21 - 25

* = Atropine 20 mg/kg body weight (= Atropine Sulfate 24 mg/kg body weight)

TREATMENT WITH TEST OR CONTROL ARTICLES

Method	Intraperitoneal, after overnight fasting, by slow injection.
Rationale	Requested by the Sponsor
Frequency of application	Once
Dose levels (Dose volume)	Group 1: Vehicle (10ml/kg) Group 2: 0.25% solution (10ml/kg) Group 3: 0.5 % solution (10ml/kg) Group 4: 1.0 % solution (10ml/kg)
Dose level rationale	Based on acute toxicity studies with the test material
Vehicle	Saline (0.9% NaCl solution)
Vehicle source	[redacted]
Test article preparation	The test article was weighed into a glass beaker on a tared precision balance and the vehicle added. The mixture was prepared using an agitator. During the administration period, homogeneity was maintained using a magnetic stirrer.
Frequency of preparation	Once, just prior to treatment.

TREATMENT WITH REFERENCE SUBSTANCE

Identification	Atropine (Atropine Sulfate)
Method	Intraperitoneal, after overnight fasting
Rationale	A pretreatment with Atropine Sulfate i.p. is known to inhibit gastrointestinal peristalsis in mice.

PROJECT 239117
DEXTRIN 20

Frequency of application	Once
Dose level	Group 5: 20 mg/kg body weight (= 24 mg Atropine sulfate/kg)
Dose level rationale	Commonly used in studies of this type
Dose volume	10 ml/kg body weight
Vehicle	Saline (0.9% NaCl solution)
Atropine Sulfate source	—
Vehicle source	—

TREATMENT WITH CHARCOAL

Method	Oral, by gavage
Frequency of application	Once, 60 minutes after test or control articles or Atropine treatment
Dose volume	0.3 ml/animal
Vehicle	Distilled water
Charcoal source	—
Preparation of charcoal	2 g of charcoal and 1 g of arabic gum were weighed into a mortar, then 20 ml of vehicle were added and mixed with the pestle. The suspension obtained was than transferred into a glass beaker. During the administration period, homogeneity was maintained using a magnetic stirrer.
Frequency of preparation	Once, just prior to treatment with the test or control articles or atropine.

NECROPSY

Sacrification	The animals were sacrificed by cervical dislocation 30 minutes after charcoal application.
Intestine preparation	The gastro-intestinal tracts were removed, immediately after the death of the animals.

OBSERVATIONS

Charcoal ratio	The length of the small intestine traversed by the charcoal, was calculated in relation to the total length of the small intestine (=100%).

Although the intent of the study design was to examine the effects of icodextrin on gastrointestinal motility in mice, the design was of very limited utility. Amounts of icodextrin (10 ml/kg of a 0.25, 0.5, & 1% solution) used were far below the levels of exposure that would be found in peritoneal dialysis (expected human dosage=~30 ml/kg of a 7.5% solution, a 21 to 84 fold higher exposure). Additionally, the reference substance, atropine, did not work in this study. Basically, it was an uncontrolled experiment using low doses of a test material. As expected, the results showed no treatment differences. However, the control animals had such a large standard deviation (24% of the total value), any effect would be difficult to interpret.

In conclusion, this poorly designed study may have shown some decrease in gastrointestinal motility, however, the large standard deviations in the controls don't allow for the conclusion that the positive control decreased gastrointestinal motility.

Abuse liability: Not Done

Other: Smooth Muscle - Project 239095: Effects on Smooth Muscles Vol. 1.7 p. 192-273
Study authors state that the methods did not respond well to dilution, and that the effects seen were negligible.

PROJECT 239095: EFFECTS ON SMOOTH MUSCLES VOL. 1.7 P. 192-273

Study title: Effects on the Respiratory and Cardiovascular Systems of the Anaesthetized Rabbit

Key study findings:

Study no: 239095
Volume #, and page #: Vol. 1.7, pages 192-273
Conducting laboratory and location: .

Date of study initiation: 11/19/1990
GLP compliance:
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Dextrin 20, Batch # QC001/B, 92.5-98.1% purity, DX084/B 92.5%
Formulation/vehicle: 0, 2.5, 5, or 10% dextrin 20 in 0.9% sterile saline

Species/strain: Albino Guinea pig

Han Wistar Rat
#/sex/group or time point (main study): 2 males (Guinea Pigs), 2 females (rats)
Age: 8 weeks (Guinea pigs), 14 weeks (rats)
Weight: 361-416 g (Guinea pigs), 238-246 g (rats)
Doses in administered units: ml/kg
Route, form, volume, and infusion rate: Intravenous, 1 ml/kg

This study was designed to test the effects of icodextrin on smooth muscle contraction. Two systems were used, 1) isolated ileum of guinea pigs and 2) isolated uterus of rats. The following pages detail the experimental setups utilized.

PROJECT 239095
DEXTRIN 20

EFFECTS ON SMOOTH MUSCLES

1) Isolated Ileum of Guinea Pigs

TEST AIM	To examine for inherent spasmogenic activity and response to spasmogens (acetylcholine, histamine and barium chloride) in the presence of the test material.
TEST SYSTEM	
Test species	Ibm: — Albino Guinea Pig (SPF)
Rationale	Commonly used test species for studies of this type
Source	
Total number of animals	4 males (main test) 1 male (pretest)
Number of animals/standard agonist	2 males
Number of animals for pretest	1 male
Age (at sacrifice)	8 weeks
Body weight range (at sacrifice)	361 - 416 g
Randomization	Randomly selected at time of delivery.
Identification	Cage number.
Animal number	Pretest: 1 Main test: 2, 3, 10 and 11
Acclimatization	28-30 days, after veterinary examination.
Room number - acclimatization - testing	 111 111
Housing	Individually in — 3 cages with softwood bedding

PROJECT 239095
DEXTRIN 20

Organ to be tested	Isolated ileum
Ileum preparation	The animals were fasted overnight in cages with raised wire floors, but allowed access to water ad libitum and then killed by cervical dislocation. The ileum was carefully removed. Longitudinal strips (2-3 cm length) were transferred into Tyrode solution and stored at 4 degrees centigrade until analysis (~24 hours after organ isolations). The ileum strips were then fixed in the organ bath and pre-stretched (tension approximately 1 gram).
Number of strips/standard agonist	Four strips of the ileum (two from each animal).
Organ bath	Four glass containers filled with 10 ml Tyrode solution at 37.5 degrees centigrade, gently aerated with 95 % O_2 and 5 % CO_2.
Recorder	Grass Polygraph paper Recorder Type —— with force displacement transducer. ——

TREATMENT WITH TEST ARTICLE

Test article concentrations	25, 10, 5 and 2.5%
Rationale	Based on the results of a pretest carried out to establish the dose range.
Dose volume (for Histamine and Acetylcholine):	25% = 10 ml 25% DEXTRIN 20 10% = 4 ml 25% DEXTRIN 20 + 6 ml Tyrode 5% = 2 ml 25% DEXTRIN 20 + 8 ml Tyrode 2.5% = 1 ml 25% DEXTRIN 20 + 9 ml Tyrode
Dose volume (for Barium-chloride)	25% = 5 ml 50% DEXTRIN 20 + 5 ml Tyrode 10% = 2 ml 50% DEXTRIN 20 + 8 ml Tyrode 5% = 1 ml 50% DEXTRIN 20 + 9 ml Tyrode 2.5% = 0.5 ml 50% DEXTRIN 20 + 9.5 ml Tyrode
Dosing procedure	The test article solutions were added to the organ bath in ascending dose order.
Vehicle	Tyrode solution.
Test article preparation	The test article was weighed into a glass beaker on a tarred precision balance and the vehicle added. The mixture was prepared using an agitator. During administration period, homogeneity was maintained using a magnetic stirrer.
Frequency of preparation	Once, just prior to treatment.

PROJECT 239095
DEXTRIN 20

STANDARD AGONISTS

Histamine

The following sequence of histamine concentrations in the organ bath solution was tested:

0.0001	µg/ml	(10^{-10} g/ml)
0.001	µg/ml	(10^{-9} g/ml)
0.01	µg/ml	(10^{-8} g/ml)
0.1	µg/ml	(10^{-7} g/ml)
1	µg/ml	(10^{-6} g/ml)

Dose volume — 0.1 ml/10 ml organ bath solution.

Source —

Vehicle — Tyrode solution.

Acetylcholine

The following sequence of acetylcholine concentrations in the organ bath solution was tested:

0.0001	µg/ml	(10^{-10} g/ml)
0.001	µg/ml	(10^{-9} g/ml)
0.01	µg/ml	(10^{-8} g/ml)
0.1	µg/ml	(10^{-7} g/ml)
1	µg/ml	(10^{-6} g/ml)

Dose volume — 0.1ml/10ml organ bath solution.

Source —

Vehicle — Tyrode solution.

Barium chloride

The following sequence of barium chloride concentrations in the organ bath solution was tested:

1	µg/ml	(10^{-6} g/ml)
3	µg/ml	(3×10^{-6} g/ml)
10	µg/ml	(10^{-5} g/ml)
30	µg/ml	(3×10^{-5} g/ml)

Dose volume — 0.1 ml/10 ml organ bath solution.

Source —

Vehicle — Bidistilled water.

PROJECT 239095
DEXTRIN 20

STANDARD ANTAGONISTS

Histamine-antagonist:

Diphenhydramine concentration	0.1 µg/ml organ bath solution.
Dose volume	0.1 ml/10 ml organ bath solution.
Source	———
Vehicle	Tyrode solution.

Acetylcholine-antagonist:

Atropine concentration	0.01 µg/ml organ bath solution.
Dose volume	0.1 ml/10 ml organ bath solution.
Source	———
Vehicle	Tyrode solution.

Bariumchloride-antagonist:

Papaverine concentration	2.5 µg/ml organ bath solution.
Dose volume	0.1 ml/10ml organ bath solution.
Source	———
Vehicle	Bidistilled water.

PROJECT 239095
DEXTRIN 20

PROCEDURE

General Procedure	About five minutes after obtaining at least three constant concentration-response curves for each standard agonist (histamine, acetylcholine and barium chloride) by its cumulative application, with approx. 30-60 seconds time interval between the single agonist concentrations and a wash out period befor the next application of the standard agonist, the test article (beginning with the lowest concentration) suspendend in its corresponding vehicle was applied to the organ bath. After another five minutes the concentration-response curve for the agonist was redetermined, and the effect of each test article concentration was assessed.
Antagonist activity	Antagonist activity exerted by the test article was compared with that seen with standard antagonists (diphenhydramine, atropine or papaverine).

PROJECT 239095
DEXTRIN 20

2) Isolated Uterus of Rats

TEST AIM	To examine for inherent spasmogenic activity and response to spasmogen (oxytocin) in the presence of the test material
TEST SYSTEM	
Test species	Wan Wistar Rat, outbred, SPF Quality.
Rationale	Commonly used test species for studies of this type
Source	———
Total number of animals	2 females (main test) 1 female (pretest)
Number of animals/standard agonist	2 females
Number of animals for pretest	1 female
Age (at sacrifice)	14 weeks
Body weight range (at sacrifice)	238 and 246 g
Identification	Fur color codes with indelible felt-tip pen.
Animal number	Pretest: 6 Main test: 7 and 8
Acclimatization	31 days, after veterinary examination.
Randomization	Randomly selected at time of delivery.
Room number - acclimatization - testing	———
Housing	By three in ——— 3 cages with softwood bedding ———

PROJECT 239095
DEXTRIN 20

Organ to be treated	Isolated uterus
Uterus preparation	The animals were killed by cervical dislocation. The uterus was removed and each horn was fixed in the organ bath and pre-stretched (tension approximately 1 gram).
Number of strips/standard agonist	Four strips of the uterus (two from each animal).
Organ bath	Four glass containers filled with 10 ml Jalon solution at 32°C, gently aerated with 95 % O_2 and 5 % CO_2.
Recorder	Grass Polygraph paper Recorder —— with force displacement transducer —

TREATMENT WITH TEST ARTICLE

Test article concentrations	25, 10, 5 and 2.5 %
Rationale	Based on the results of pretest and requested by the sponsor.
Dose volume	25% = 10 ml 25% DEXTRIN 20 10% = 4 ml 25% DEXTRIN 20 + 6 ml Jalon 5% = 2 ml 25% DEXTRIN 20 + 8 ml Jalon 2.5% = 1 ml 25% DEXTRIN 20 + 9 ml Jalon
Dosing procedure	The test article solutions were added to the organ bath in ascending dose order.
Vehicle	Jalon solution
Test article preparation	The test article was weighed into a glass beaker on a tared precision balance and the vehicle added. The mixture was prepared using an agitator. During administration period, homogeneity was maintained using a magnetic stirrer.
Frequency of preparation	Once, just prior to treatment.

STANDARD AGONIST

Oxytocin concentrations	The following sequence of oxytocin concentrations in the organ bath solution was tested:

0.001	µg/ml	(10^{-9} g/ml)
0.01	µg/ml	(10^{-8} g/ml)
0.1	µg/ml	(10^{-7} g/ml)
1	µg/ml	(10^{-6} g/ml)
10	µg/ml	(10^{-5} g/ml)

Dose volume	0.1 ml/10 ml organ bath solution.
Source	[redacted]
Vehicle	Jalon solution.

PROCEDURE

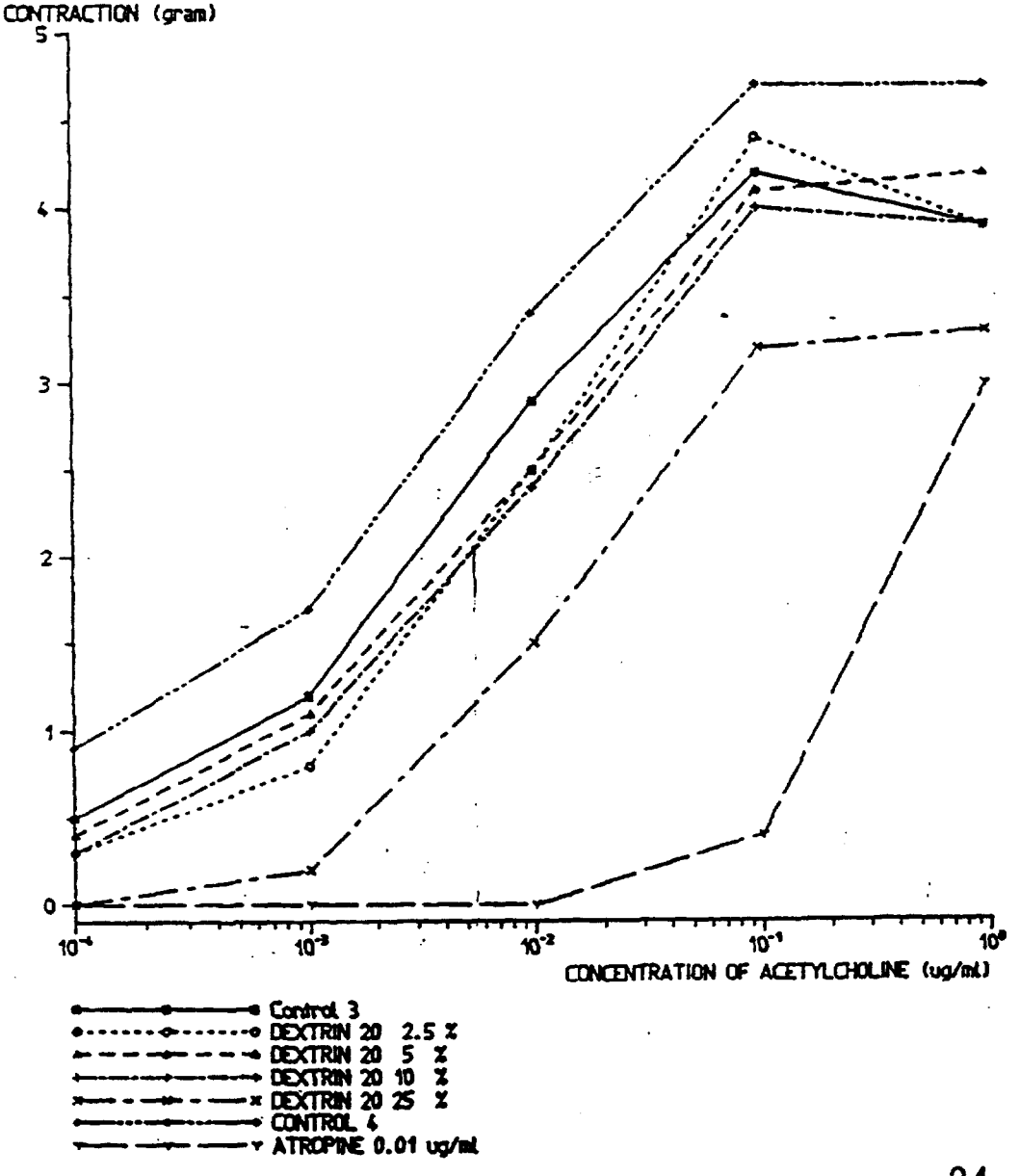
General Procedure	About five minutes after obtaining at least three constant concentration-response curves for oxytocin by its cumulative application, with approx. one minute time interval between the single oxytocin concentrations and a wash out period befor the next application of the standard agonist, the test article (beginning with the lowest concentration) suspendend in its corresponding vehicle was applied to the organ bath. After another five minutes the concentration-response curve for the agonist was redetermined, and the effect of each test article concentration was assessed.

The results consistently show that 25% icodextrin is inhibitory in all the preparations. However, the study authors state "the test system is not designed to produce pharmacologically reliable data after replacement of more than 10% of the original bath solution." In addition, there are the changes in the viscosity of the medium due to the high concentration of icodextrin. Otherwise, only the acetylcholine-induced contractions in guinea pig ileum and the oxytocin-induced contractions in rat uterus preparations displayed an inhibition at 5 and 10% of icodextrin, physiologically relevant concentrations. 5 and 10% icodextrin shifted acetylcholine responsiveness almost 2-fold in the guinea pig ileum system, and oxytocin responsiveness 2-fold in the rat uterus system.

In conclusion, icodextrin does seem to display some inhibition in 2 of the 4 smooth muscle systems tested. However, a 2-fold concentration shift is small enough to probably not be physiologically relevant except in individuals with some underlying condition related to neuro-transmitter concentration.

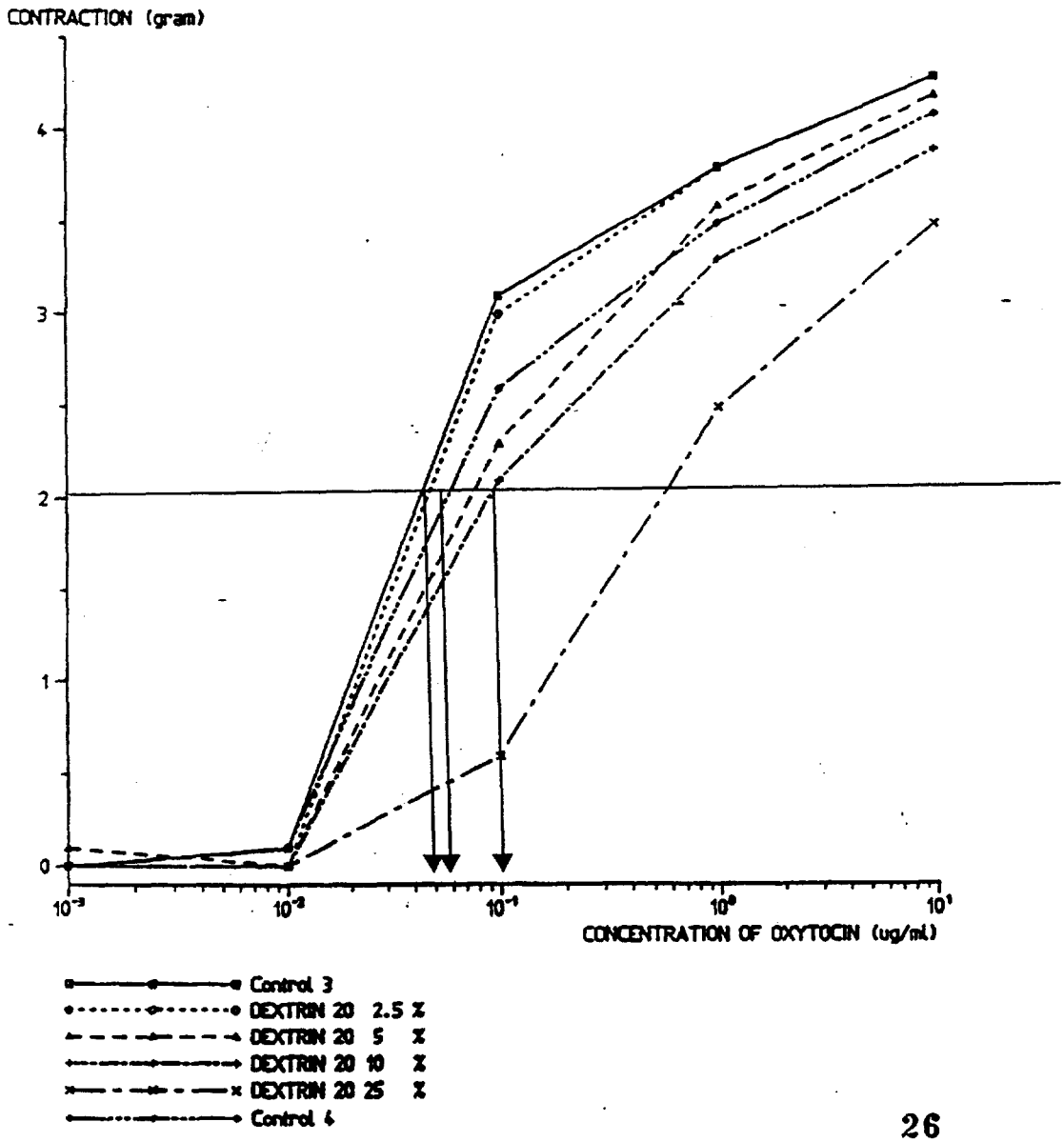
1) ISOLATED ILEUM OF GUINEA PIGS

Acetylcholine-induced contractions (mean values)
(4 organ strips / 2 strips per animal)



2) ISOLATED UTERUS OF RATS

Oxytocin-induced contractions (mean values)
(4 organ strips / 2 strips per animal)



General Safety Pharmacology Study:

STUDY TITLE: **GENERAL PHARMACOLOGY OF ICODEXTRIN**

Key study findings:

Study no: 7L828
Volume #, and page #: vol 1.7 p.281-328
Conducting laboratory and location: [redacted]

Date of study initiation: 11/20/1990
GLP compliance:
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Dextrin 20, Batch # QC001/B, 92.5-98.1% purity
Formulation/vehicle: 0, 2.5, 5, or 10% dextrin 20 in 0.9% sterile saline

Dosing:

Species/strain: New Zealand White Rabbit
#/sex/group or time point (main study): 2 males
Age: 15-17 weeks
Weight: 2.595 – 2.713 kg
Doses in administered units: ml/kg
Route, form, volume, and infusion rate: Intravenous, 1 ml/kg

This study was to evaluate the general pharmacological effects of icodextrin in a non-clinical safety study. Effects on general behavior, the central nervous system, sleeping time (pentobarbital induced), drug induced convulsions, analgesia, body temperature, respiratory and cardiovascular systems, gastrointestinal tract and excretion of urine and urinary electrolytes were studied. Intraperitoneal fluid dosages were 40 ml/kg, slightly above the 33.3 ml/kg that would be a standard human dose (2000 ml/ 60 kg). Electrolyte solutions (PD-2) were 0.445% L-sodium lactate, 0.538% sodium chloride, 0.0257% calcium chloride dihydrate and 0.00508% magnesium chloride hexahydrate at a pH of 5.40-5.55. Unfortunately, none of the experiments were done with a neutral pH solution, or even untreated animals. Therefore, there were no adequate controls.

Effects on general behavior were performed in mice. The treatment groups were electrolyte solution, 2.27% glucose (Dianeal), 7.5% icodextrin and 25% icodextrin. All groups showed a reduction in spontaneous motor activity, with complete recovery within 6 hrs.

Effects on the central nervous system, spontaneous motor activity. All groups displayed a decline in spontaneous motor activity from approximately 2 to 9 hours post-intraperitoneal injection. Unfortunately, there is no true control, and the decline in spontaneous motor activity could presumably be a normal part of the mouse diurnal cycle. Time of administration, nor the normal daily motor activity pattern is given.

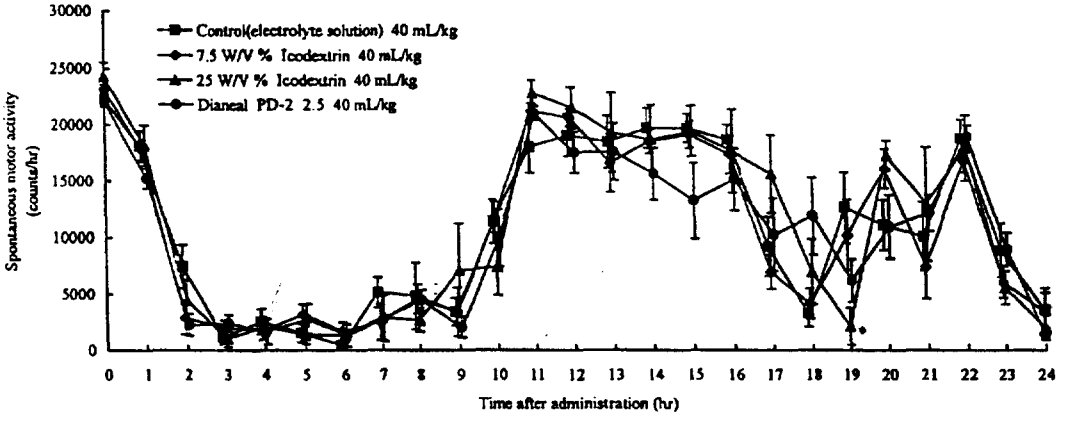
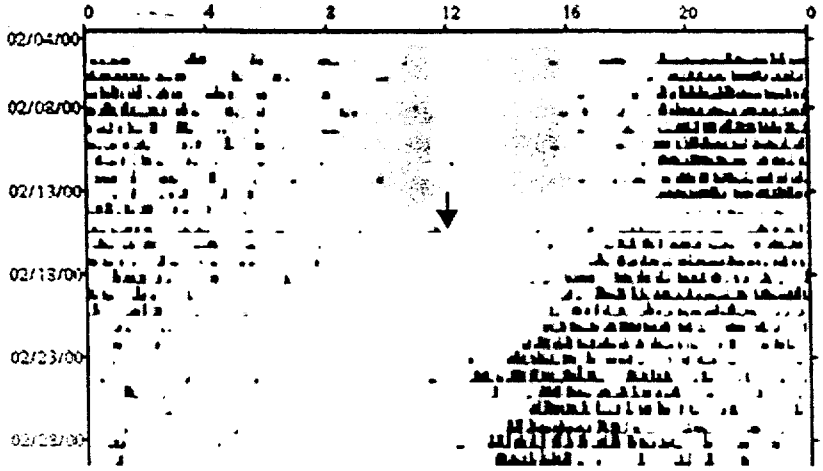


Fig. 1 Effects of intraperitoneally administered Icodextrin and Dianeal PD-2 2.5 on spontaneous motor activity in mice
Each point and bar represents the mean ±S.E. of 3 mice
* : Significantly different from the control in Dunnett's test at $p < 0.05$
Drug administration : 9 : 52

Wheel-running activity in mice



In a 12:12 light:dark cycle, onset of activity in mice is coincident with 'lights off'.

In the absence of external stimuli, activity onsets are set by the central pacemaker (SCN)

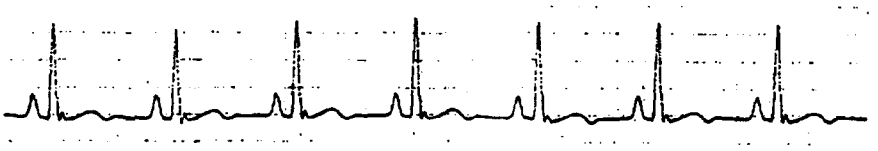
Brief light pulses at distinct phases of the

Table 9 Effects of intraperitoneally administered Icodextrin and Dianeal PD-2 2 5 on body temperature in rats

Drugs (40 mL/kg i.p.)	Animal No.	Rectal temperature (℃) Before	Time after administration (hr) 0.5	1	2	4	6	12	24
Control (electrolyte solution)	A-1								
	A-2								
	A-3								
	A-4								
	A-5								
	A-6								
	Mean	38.2	38.2	38.2	38.1	37.8	37.7	38.0	37.5
	S.E.	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1
Icodextrin (7.5 w/v %)	B-1								
	B-2								
	B-3								
	B-4								
	B-5								
	B-6								
	Mean	38.0	38.1	38.1	37.9*	37.8	38.1	38.0	37.4
	S.E.	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Icodextrin (25 w/v %)	C-1								
	C-2								
	C-3								
	C-4								
	C-5								
	C-6								
	Mean	38.2	38.3	38.2	38.0	38.5	38.3	38.0	37.6
	S.E.	0.1	0.1	0.1	0.1	0.2	0.3	0.1	0.1
Dianeal PD-2 2.5	D-1								
	D-2								
	D-3								
	D-4								
	D-5								
	D-6								
	Mean	38.2	38.2	38.1	37.9	37.8	37.6	38.2	37.5
	S.E.	0.1	0.1	0.0	0.0	0.1	0.1	0.2	0.1

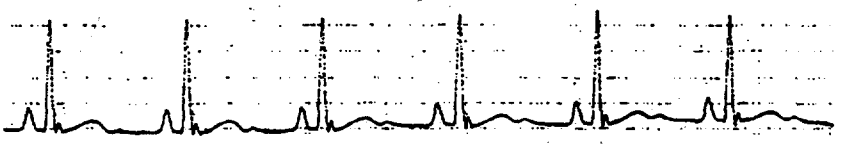
Effects on respiratory and cardiovascular systems: Unfortunately, only lead II data from the ECG was reported. These results do show a lengthening in the QT interval and the QTc. The merging of the T and U waves creates difficulties in assessing the QT interval, since the end of the T wave is part of the U wave. Potential irregularities occurred in the production of U waves which are indicative of electrolyte imbalances. However, the lack of an adequate control does not allow a definitive understanding of what is happening. Acidosis, which could be induced by the intraperitoneal infusion of a large volume of a pH 5.4 solution, is known to cause electrolyte imbalance, although more commonly hypokalemia. The ionic imbalance is probable since examination of urinary excretions shows significant retention of sodium, potassium and chloride ions in the rats. This is interesting in that it has been hypothesized that sudden death in the dialysis patient population correlates with the prolonged QT dispersion in this population.

Before



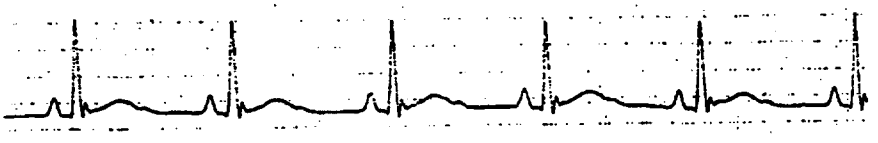
Electrolyte Solution

120 min



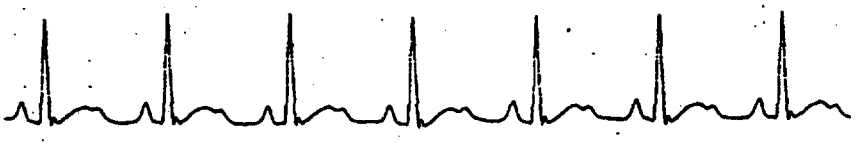
7.5% Icodextrin

120 min



25% Icodextrin

120 min



No other significant effects of icodextrin on respiratory or cardiovascular systems were noted. However, the respiratory studies were done on anesthetized dogs treated with isoflurane and thiopentin, two drugs known to cause respiratory depression.

Effects on gastrointestinal tract: no effects reported.

Effects on excretions of urine and urinary electrolytes:

Results showed significant reductions in urinary volume and electrolyte excretion for 7.5% and 25% icodextrin treatment compared to the electrolyte control and dianeal treatment.

Table 17 Effects of intraperitoneally administered Icodextrin and Dianeal PD-2 2.5 on urine excretion in saline loaded rats

Drugs (40 mL/kg i.p.)	Animal No.	Cumulative urine volume (mL) Time after administration (hr) 1	2	3	4	5	6	7	8	9	10	11	12
Control (electrolyte solution)	A-1												
	A-2												
	A-3												
	A-4												
	A-5												
	A-6												
	Mean	0.8	2.5	3.9	4.8	5.8	6.5	8.0	8.5	9.6	10.4	11.5	11.8
	S.E.	0.3	0.6	0.6	0.9	0.7	0.6	0.8	0.7	0.9	1.0	0.8	0.8
Icodextrin (7.5 w/v %)	B-1												
	B-2												
	B-3												
	B-4												
	B-5												
	B-6												
	Mean	0.4	0.9	0.9	1.1*	1.5*	1.8*	2.0*	2.4*	2.9*	3.5*	4.4*	5.5*
	S.E.	0.2	0.3	0.3	0.2	0.4	0.4	0.3	0.3	0.3	0.5	0.7	1.0
Icodextrin (25 w/v %)	C-1												
	C-2												
	C-3												
	C-4												
	C-5												
	C-6												
	Mean	0.2	0.5*	1.1*	2.1*	2.5*	2.7*	2.7*	2.7*	3.0*	3.2*	3.5*	3.7*
	S.E.	0.1	0.3	0.8	1.4	1.7	1.6	1.6	1.6	1.7	1.7	2.0	1.9
Dianeal PD-2 2.5	D-1												
	D-2												
	D-3												
	D-4												
	D-5												
	D-6												
	Mean	0.5	1.6	2.3	3.0	3.4	4.0	4.1	5.0	6.0	7.4	8.2	8.5
	S.E.	0.3	1.1	1.5	1.7	1.8	1.7	1.7	1.6	1.7	2.0	1.9	2.0

* : Significantly different from the control in Dunnett's test at $P < 0.05$

Table 18 Effects of intraperitoneally administered Icodextrin and Dianeal PD-2 2.5 on urinary electrolyte excretion in saline loaded rats

Drugs (40 mL/kg i.p.)	Animal No.	Electrolytes (mmol/12hr) Na^+	K^+	Cl^-
Control (electrolyte solution)	A-1			
	A-2			
	A-3			
	A-4			
	A-5			
	A-6			
	Mean	1.19	0.62	1.30
	S.E.	0.11	0.04	0.09
Icodextrin (7.5 w/v %)	B-1			
	B-2			
	B-3			
	B-4			
	B-5			
	B-6			
	Mean	0.48	0.56	0.56
	S.E.	0.09	0.06	0.06
Icodextrin (25 w/v %)	C-1			
	C-2			
	C-3			
	C-4			
	C-5			
	C-6			
	Mean	0.40	0.25*	0.47*
	S.E.	0.24	0.05	0.21
Dianeal PD-2 2.5	D-1			
	D-2			
	D-3			
	D-4			
	D-5			
	D-6			
	Mean	0.88	0.52	0.99
	S.E.	0.22	0.04	0.18

* : Significantly different from the control in Dunnett's test at $P < 0.05$

Mention spontaneous motor activity reduced, icodextrin inhibits some smooth muscle

Effects of Intraperitoneal Administration of Icodextrin on the circulating blood volume and blood electrolytes in rats

This study utilized Sprague-Dawley rats that were 5 weeks old, weighing between 157.2 and 227.2 g. Treatments were with 200 ml/kg one time injection intraperitoneally of 1) saline, 2) elctrolyte solution, 3) 7.5% icodextrin, 4) 25% icodextrin, and 5) dianeal PD-2. Animals were injected and followed for 24 hrs. At 3, 6, and 24 hours samples were collected for determination of blood volume and electrolyte levels.

Icodextrin had significant effects on blood volume and electrolyte levels. The electrolyte solution, 7.5% icodextrin, and 25% icodextrin all gave a significant reduction ($p<.01$) in blood volume at the 24 hour timepoint over the untreated animal level. At 6 hours, 25% icodextrin was significantly different from saline controls and untreated ($p<.01$), while the dianeal treatment was significantly different from the untreated animals. At 3 hours, the saline and 7.5% icodextrin treaments showed an increase in blood volume over untreated animals ($p<.01$), dianeal treatment was different from the saline treated controls ($p<.01$), but not from the untreated animals; and 25% icodextrin was significantly different from the saline and untreated controls ($p<.01$). See Table I for a summary of the results.

These results are somewhat postulated owing to the deficiencies in the data. For example, a 200 g rat, as was used in this study, should have a total blood volume of 12 ml, or 60 ml/kg. The study reports blood volumes of 40.4 to 182.8 ml/kg. 40 ml of fluid was injected intraperitoneally to each animal. In the study, animals are reported as having a blood volume of 115 ml/kg prior to receiving 40 ml ip. The icodextrin treated rats were shown to have decreased their blood volumes, while other studies have shown that icodextrin treatment reduces urinary output dramatically at the same dose range. Of primary interest is that the electrolyte solution does alter serum chemistry compared to saline solution at neutral pH. Unfortunately, many of the studies used the electrolyte solution for controls, which makes it more difficult to determine whether effects seen are due to the electrolyte solution or icodextrin.

Comparison with the historical controls for CRL SD rats shows that the control rats have low serum calcium and potassium values to begin with, indicating potential problems with the population. This indicates results must be examined with caution.

Table 1 Effects of intraperitoneal administration of Icodextrin and electrolyte solution on circulating blood volume in rats

Dose	Time after administration (hr)		
	3	6	24
None 115.9±2.8 (31)			
Saline	150.1±12.0** (6)	122.9± 9.6 (6)	100.5± 8.0 (6)
Electrolyte solution	112.5± 5.8# (6)	131.9± 7.1 (5)*	84.1±13.7** (6)
7.5 % Icodextrin	143.0±11.2** (6)	101.0± 6.9 (6)	81.5±13.1** (6)
25 % Icodextrin	91.5± 5.5**## (6)	67.8± 6.6**## (5)*	77.0± 8.6** (6)
PD-2 2.5	98.5± 7.1## (7)	96.6± 9.8# (7)	103.6± 8.3 (7)

Saline, Electrolyte solution, 7.5 % Icodextrin, 25 % Icodextrin, and PD-2 2.5 were injected at 200 mL/kg.
Values are means±S.E. (mL/kg). Numbers of animals are in parentheses.
*Abnormal data were omitted.
#P<0.05, **P<0.01, significantly different from the value in untreated animals (Dunnett's test)
##P<0.05, ##P<0.01, significantly different from the time-matched value in saline-injected group (Dunnett's test)

Table 2 Effects of intraperitoneal administration of Icodextrin and electrolyte solution on plasma sodium level in rats

Dose	Time after administration (hr)		
	3	6	24
None 141.5±0.2 (31)			
Saline	141.4±0.2 (6)	139.2±0.5** (6)	143.0±0.3** (6)
Electrolyte solution	142.1±0.3 (6)	138.3±0.4** (6)	142.5±0.4 (6)
7.5 % Icodextrin	139.8±0.8# (6)	139.6±0.4** (6)	142.3±0.4 (6)
25 % Icodextrin	139.8±3.4 (5)*	131.3±1.9**## (6)	130.3±4.9**## (6)
PD-2 2.5	140.5±0.7 (7)	140.1±0.5 (7)	140.9±0.4 (7)

Saline, Electrolyte solution, 7.5 % Icodextrin, 25 % Icodextrin, and PD-2 2.5 were injected at 200 mL/kg.
Values are means±S.E. (mEq/L). Numbers of animals are in parentheses.
*In one animal, sufficient amount of plasma for determination of electrolyte level could not be obtained.
#P<0.05, **P<0.01, significantly different from the value in untreated animals (Dunnett's test)
##P<0.01, significantly different from the time-matched value in saline-injected group (Dunnett's test)

Table 3 Effects of intraperitoneal administration of Icodextrin and electrolyte solution on plasma potassium level in rats

Dose	Time after administration (hr)		
	3	6	24
None	4.23±0.04 (31)		
Saline	4.02±0.12 (6)	3.96±0.12 (6)	4.11±0.07 (6)
Electrolyte solution	4.48±0.15 (6)	4.77±0.18** (6)	3.84±0.11* (6)
7.5 % Icodextrin	4.29±0.16 (6)	3.94±0.02 (6)	4.11±0.16 (6)
25 % Icodextrin	4.53±0.36 (5)[a]	5.59±0.26$^{**\#\#}$ (6)	6.06±0.71$^{**\#\#}$ (6)
PD-2 2.5	4.40±0.22 (7)	4.40±0.37 (7)	4.54±0.19 (7)

Saline, Electrolyte solution, 7.5 % Icodextrin, 25 % Icodextrin, and PD-2 2.5 were injected at 200 mL/kg.
Values are means±S.E. (mEq/L). Numbers of animals are in parentheses.
[a] In one animal, sufficient amount of plasma for determination of electrolyte level could not be obtained.
*P<0.05, **P<0.01, significantly different from the value in untreated animals (Dunnett's test)
$^{\#\#}$P<0.01, significantly different from the time-matched value in saline-injected group (Dunnett's test)

Table 4 Effects of intraperitoneal administration of Icodextrin and electrolyte solution on plasma chloride level in rats

Dose	Time after administration (hr)		
	3	6	24
None	104.6±0.2 (31)		
Saline	107.1±0.5** (6)	102.7±0.5** (6)	104.3±0.3 (6)
Electrolyte solution	104.8±0.3 (6)	101.8±0.8** (6)	104.6±0.6 (6)
7.5 % Icodextrin	103.3±0.8 (6)	101.1±0.6** (6)	104.2±0.1 (6)
25 % Icodextrin	102.3±3.9 (5)[a]	93.1±2.1$^{**\#\#}$ (6)	92.7±4.7$^{**\#\#}$ (6)
PD-2 2.5	102.5±0.5** (7)	102.5±1.0** (7)	103.8±0.5 (7)

Saline, Electrolyte solution, 7.5 % Icodextrin, 25 % Icodextrin, and PD-2 2.5 were injected at 200 mL/kg.
Values are means±S.E. (mEq/L). Numbers of animals are in parentheses.
[a] In one animal, sufficient amount of plasma for determination of electrolyte level could not be obtained.
**P<0.01, significantly different from the value in untreated animals (Dunnett's test)
$^{\#\#}$P<0.01, significantly different from the time-matched value in saline-injected group (Dunnett's test)

Table 5 Effects of intraperitoneal administration of Icodextrin and electrolyte solution on plasma calcium level in rats

Dose	Time after administration (hr)		
	3	6	24
None	8.9±0 (31)		
Saline	7.6±0.1** (6)	7.5±0.2** (6)	9.2±0.1 (6)
Electrolyte solution	8.7±0.1## (6)	8.3±0.1**,# (6)	9.4±0.1** (6)
7.5 % Icodextrin	8.9±0.2## (6)	8.5±0.1**,## (6)	9.2±0.1 (6)
25 % Icodextrin	9.4±0.2## (5)*	9.3±0.2## (6)	8.9±0.4 (6)
PD-2 2.5	8.8±0.3## (7)	8.9±0.2## (7)	9.1±0.1 (7)

Saline, Electrolyte solution, 7.5 % Icodextrin, 25 % Icodextrin, and PD-2 2.5 were injected at 200 mL/kg.
Values are means±S.E. (mg/dL). Number of animals are in parentheses.
*In one animal, sufficient amount of plasma for determination of electrolyte level could not be obtained.
**P<0.01, significantly different from the value in untreated animals (Dunnett's test)
#P<0.05, ## P<0.01, significantly different from thetime-matched value in saline-injected group (Dunnett's test)

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Table 7: Summary of Serum Chemistry Parameters from Individual Studies at 4 Weeks – Males
Study. CRL historical control data.

Identification		StudyA		StudyB		StudyC		StudyD
StudyStartDate		Oct-96		May-97		Apr-97		Nov-96
NumberofAnimals		15		15		15		15
space	Mean	+/-S.D.	Mean	+/-S.D.	Mean	+/-S.D.	Mean	+/-S.D.
A/GRatio	1.4	0.1	1.4	0.1	1.3	0.1	1.4	0.1
Albumin, _g/dl	3.4	0.1	3.4	0.1	3.2	0.1	3.5	0.1
AlkalinePhosphatase,u/l	255	50	219	35	212	59	225	49
ALT,u/l	35	4	29	4	29	5	28	5
AST,u/l	113	20	102	15	101	17	116	23
Calcium, mg/dl	9.9	0.2	9.4	0.2	9.7	0.2	10	0.3
Chloride, mEq/l	104	1	102	1	104	1	103	1
CholesterolTotal,mg/dl	64	10	65	11	65	12	64	6
Creatinine,mg/dl	0.6	0.1	0.5	0	0.5	0.1	0.6	0.1
Glucose, mg/dl	158	20	138	16	144	22	162	22
Phosphorus,mg/dl	9.2	0.5	8.5	0.4	8.6	0.3	9.4	0.3
Potassium,mEq/l	5.2	0.2	4.8	0.3	4.9	0.2	5.2	0.4
Sodium, mEq/l	144	1	141	1	142	1	142	1
TotalProtein,g/dl	5.8	0.2	5.9	0.2	5.8	0.3	5.9	0.2
Triglycerides,mg/dl	53	16	53	15	72	26	60	27
UreaNitrogen,mg/dl	12	2	13	2	12	1	13	

Results of blood volume and electrolyte study in rats. + indicates value higher than untreated, - indicates lower value ++ or -- indicates significant at p<.01, + or - indicates significant at p<.05

	Blood Volume			Sodium			Potassium			Calcium			Chloride			Hematocrit		
Hours	3	6	24	3	6	24	3	6	24	3	6	24	3	6	24	3	6	24
Saline	++				--	++				--	--		++	--		-		
Electrolyte	+		--		--			++	-	++	++	++		--				
7.5% Icodextrin	++		--	-	--					++	++			--			+	
25% Icodextrin	--	--	--		--	--		++	++	++	++			--	--	++	++	++
Dianeal PD-2	--	-								++	++		--	--		++	+	

Safety pharmacology summary & conclusions: Most of the studies showed little or no effect of icodextrin in animal studies. Many of these studies were done with icodextrin in distilled water, 0.9 % NaCl, or cell culture media, not with the proposed vehicle, PD-2 electrolytes at pH 5-6. Concern arises over the cardiovascular results in the General Pharmacology study, which displayed an emerging U wave and with increasing icodextrin dosage, a merging of the T and U waves. Sudden cardiac death is a concern in the dialysis population, along with a prolonged QT dispersion. This study showed the appearance of a U wave in the ECG and merging of the T and U waves and a prolongation of the QT interval. This generally indicates a problem with ions, and coupled with the urinary system results showing changes in excretion raises concerns in kidney and excretory function with icodextrin.

PHARMACOKINETICS/TOXICOKINETICS:

Briefly, the concerns for this drug are different from many others since the drug is intended for peritoneal dialysis and is a large volume parenteral solution (LVPS). The drug substance, icodextrin, is in an electrolyte solution vehicle that is at pH 5.0-5.5. For dosing, the drug substance is used as a 7.5% solution, and approximately 2 L is put into the peritoneal cavity via an in-dwelling catheter. After several hours, the solution is exchanged for a fresh solution. Icodextrin is presently only intended for the long dwell (either during the workday or overnight) period.

Review of Estella Barry for IND —

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PHARMACOKINETICS (Vol 6)

Icodextrin is a substrate for α-amylase (found in pancreatic juice, saliva and plasma); the enzyme hydrolyzes icodextrin to oligosaccharides such as maltose, maltotriose, and maltotetrose. These saccharides are further metabolized to glucose by specific enzymes found in a variety of tissues.

The drug sponsor acknowledges that ideally, studies of the disposition of icodextrin should be conducted with radio-labelled polymer. However, because of difficulties of growing maize in an atmosphere of $^{14}CO_2$ and isolation of starch and other chemical procedures, this approach was ruled out.

An assay was developed to separate and analyses icodextrin/metabolites in plasma, urine and collected dialysis fluid. The assay method is briefly described in the submission. Analysis was performed in [redacted] (Repeat dose studies in rat and dog were conducted in [redacted]

1. RAT (Blood/urine samples taken from rats described in Study Report No. 7423 above.)

Briefly, blood and urine (collected over 24-hr) samples were collected from 2 rats/sex/group 24 hrs after the first dose, and 24 hrs after the first dose on day 28 the last day of treatment. Attempts to recover peritoneal fluid (prior to dosing) was collected only from rats showing abdominal discomfort.

Results

Drug sponsor reported that analysis of the plasma samples collected showed that there was no difference in the total levels of carbohydrate components (and no elevation of individual oligomer consisting of 1 to 10 glucose units or high molecular weight (HMW) fractions above 10 glucose units) of plasma in icodextrin treated rats when compared to rats treated with the electrolyte solution.

Although there was considerable inter-rat variation, urine from icodextrin treated rats showed an increase in excretion of total carbohydrate. Individual components in urine making up the total carbohydrate revealed a substantial increase in the excretion of oligomer consisting of 1-10 glucose units and HMW fraction. Recovery of total carbohydrate in urine in 24 hrs was variable, but icodextrin accounted for up to 30% of the administered dose during this period.

Drug sponsor concluded that a significant percentage of the dose of icodextrin infused in the peritoneal cavity of rats is absorbed during the dwell time of the solution. The drug sponsor asserted that in these rats, with normal renal function, icodextrin and its hydrolysis products do not accumulate and do not achieve steady

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plasma levels comparable to those seen in anephric patients treated with icodextrin solutions.

2. DOG ((Blood/urine samples taken from rats described in Study Report No. 7523 above.)

Briefly, blood and urine samples were collected only from the electrolyte solution and icodextrin groups at various intervals on days 21 and 28 of study; analysis was performed in —. Samples were collected from 2 dogs/sex/group at predose, 1, 2, 5 and 10 h (before instillation) and 24 hrs after the first instillation of the succeeding day (days 1, 7, 14, 21 and 28 of treatment.) Except for the HD icodextrin treated dogs, no attempt was made to recover peritoneal fluid. However; drug sponsor stated that the analysis was not performed because of complexity of the assay.

Failure to detect icodextrin or its metabolites in rat plasma at the LD, only plasma from the HD was studied.

Results:

Recovery of peritoneal fluid prior to infusion of each succeeding dose showed considerable inter-group variability. There was absorption of icodextrin from the peritoneal cavity as shown by the excretion of carbohydrate in urine.

Plasma samples after all treatments with icodextrin showed an increase carbohydrate levels which composed almost entirely of glucose, but also HMW material of more than 10 units of glucose.

From results obtained, drug sponsor concluded that there is a significant but variable absorption of icodextrin from the peritoneal cavity of the dog. In these dogs with normal renal function there was small accumulation of icodextrin and metabolic products in plasma on day 1 at about 5 hrs after the infusion started. A variable percentage of the infused dose of icodextrin and its metabolites were excreted in urine. Drug sponsor asserted that this route of elimination is of little or no importance in CAPD patients.

INVESTIGATOR'S BROCHURE

The nonclinical portion of the brochure appears adequate.

REPORT ON THE PHARMACOKINETIC STUDIES OF DEXTRIN 20 IN THE RAT

Basically, this study consists of blood and urine samples collected from the rats used in the 28 day toxicity study and receiving electrolyte, 14% and 20% icodextrin solution. Samples were collected on Day 1 and 28.

Blood samples were collected at 24 hours after the previous dosing. Urine samples were collected over 24 hours by housing the rats in a metabolism collection unit. The total volume was measured and an aliquot was retained for testing.

This study was not as clean as the pharmacokinetics study in dogs. Although more groups were studied (3 versus 2) than with the dog study, fewer animals were in each group. There was also more heterogeneity in the results, however, some patterns did emerge in common with the dog study. The problems may be due to using different animals for day 1 versus day 28 of the study for sampling.

Since blood levels of carbohydrate were only examined 24 hrs post dosing, this time point was useless since the dog study shows variation in peak levels of carbohydrate absorption being at 5 hours, with a return to almost normal values by 24 hours. Since there is essentially no variation in plasma carbohydrate levels among treatments and days, This portion of the study is found to be lacking, a basic time course was needed to obtain data of any value. There is some indication that plasma carbohydrate levels stabilized between days 1 and 28, potentially indicating that the rats adapted to be able to handle the higher levels of carbohydrate.

The urinary results were made less consistent by the use of different animals for the day 1 and day 28 samplings. Combined with the small sample size, that makes the results difficult to interpret. For example, the day 1 vs. day 28 results for urinary total carbohydrate are different, is this due to an adaptive response or individual variation? Urinary volume was perhaps reduced in the icodextrin groups, however, due to the high variability between the day 1 and day 28 controls, it is difficult to be certain. In addition, the data is confounded by an increase in urinary output on day 28 by the control group. This raises the question of whether the lower urinary output by the icodextrin treated rats is real or individual variation. The normal urine output for a rat is approximately 5.5 ml/100 g of body weight, in this study,

Table _ . Normal vs. Actual values of rat urinary volumes. ( ) =% deviation from normal.

Actual values:

	Electrolyte	14% Icodextrin	20% Icodextrin
Male	54.6 (+16%)	37.0 (-22%)	52.9 (+12.6%)
Female	56.1 (+87%)	30.1 (-0.5%)	36.2 (+32%)

Normal values:

	Electrolyte	14% Icodextrin	20% Icodextrin
Male	47	47.6	47
Female	30	30.25	27.5

However, one trend of interest that did arise was the level of urinary total carbohydrate (utc).

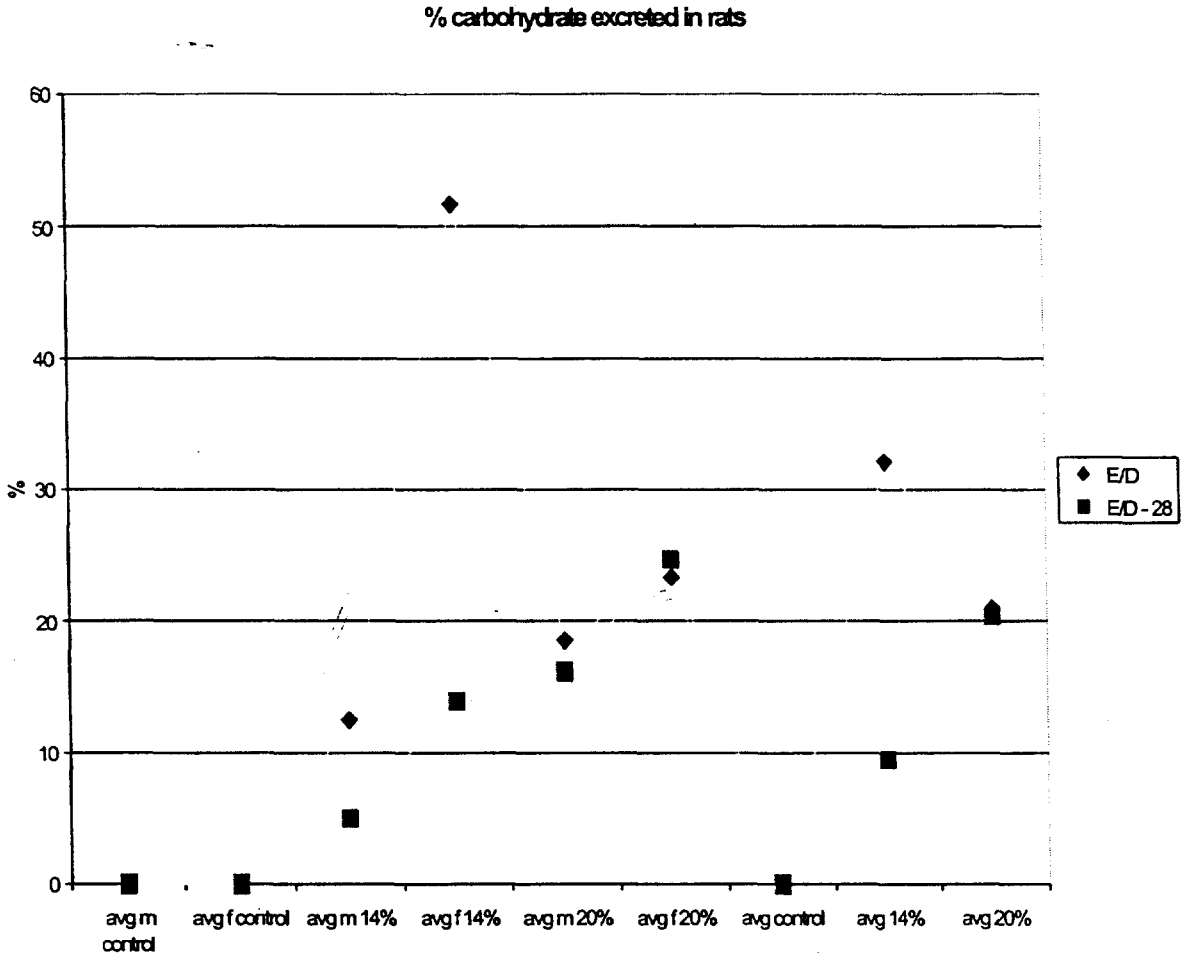


Figure ?. Carbohydrate excretion in rats.

Levels of urinary total carbohydrate increased with the dosage received by the rats. Rats receiving 14% icodextrin excreted approximately 9% of their carbohydrate dose, while rats receiving 20% icodextrin excreted 21% of their carbohydrate dose. Additionally, urinary total carbohydrate levels were higher between male and female rats receiving icodextrin, indicating a higher concentration of carbohydrate in the urine of females at the 14 and 20% dosing levels.

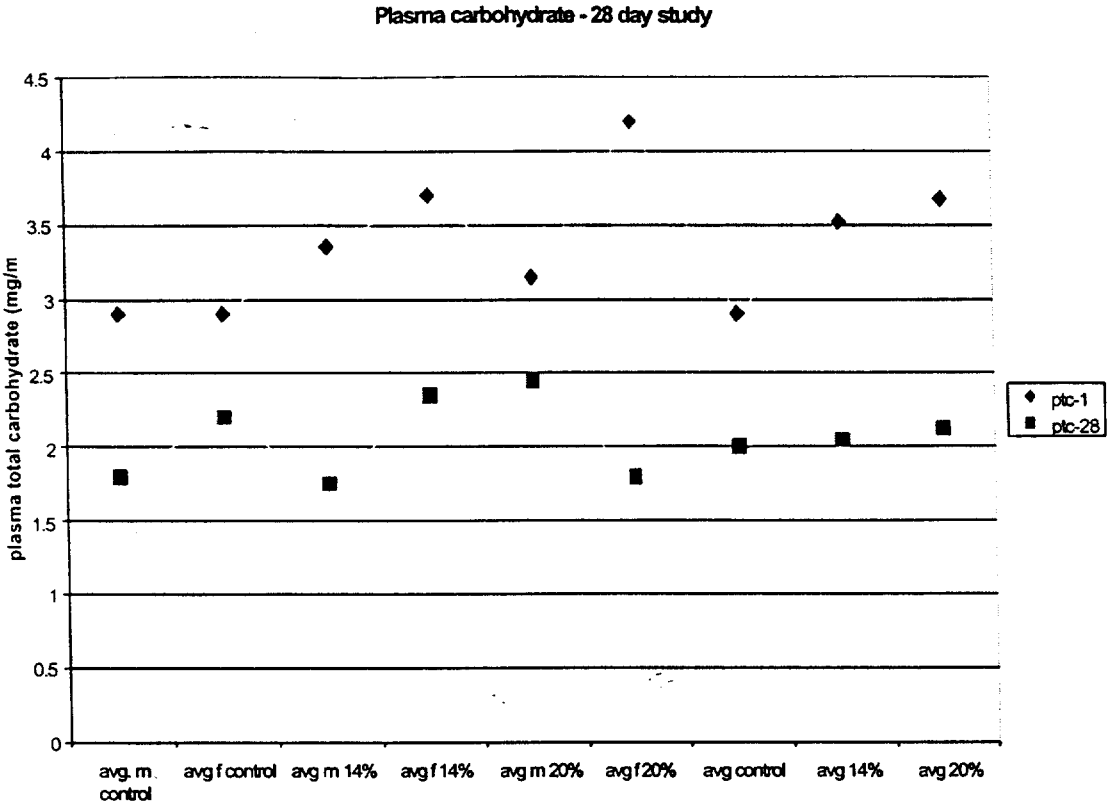


Figure _. Plasma carbohydrate values in rats.

This result is the opposite of that found in the beagle pharmacodynamics study. There are possible explanations, for example, the dogs had surgically implanted catheters that allowed easy monitoring and manipulation of the peritoneal fluid. The rats were dosed by injection, and depending on the quality of the injection, may make it impossible to determine whether fluid was actually placed peritoneally. Additionally, the dog study changed the peritoneal fluid, while the rat studied added more fluid with each dosing. The question does become what happened to the carbohydrate? Was it metabolized? This would help account for the ability of the treated rats to maintain their growth even with a 12-20% reduction in food intake. However, these studies, as done, do not provide any information to support this position.

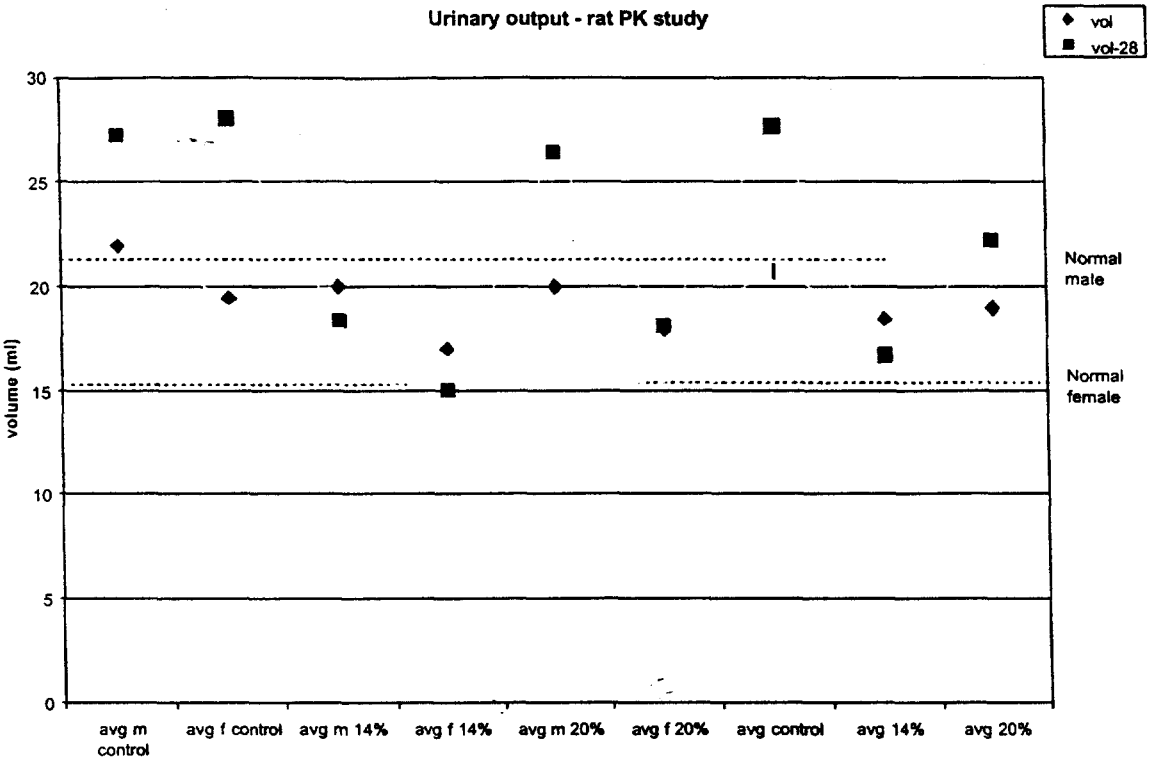


Figure _. Rat normal urinary outputs and study values.
Despite the higher than normal urinary output, water balances were positive, indicating the animals were taking in more water than they were excreting. Therefore, despite the high carbohydrate content, dehydration does not seem to be an issue in this study.

This data does support a gender difference in ability to handle peritoneally injected icodextrin. However, the study was not performed in a way that provides much information relevant to the pharmacodynamics that would be seen in a population on peritoneal dialysis.

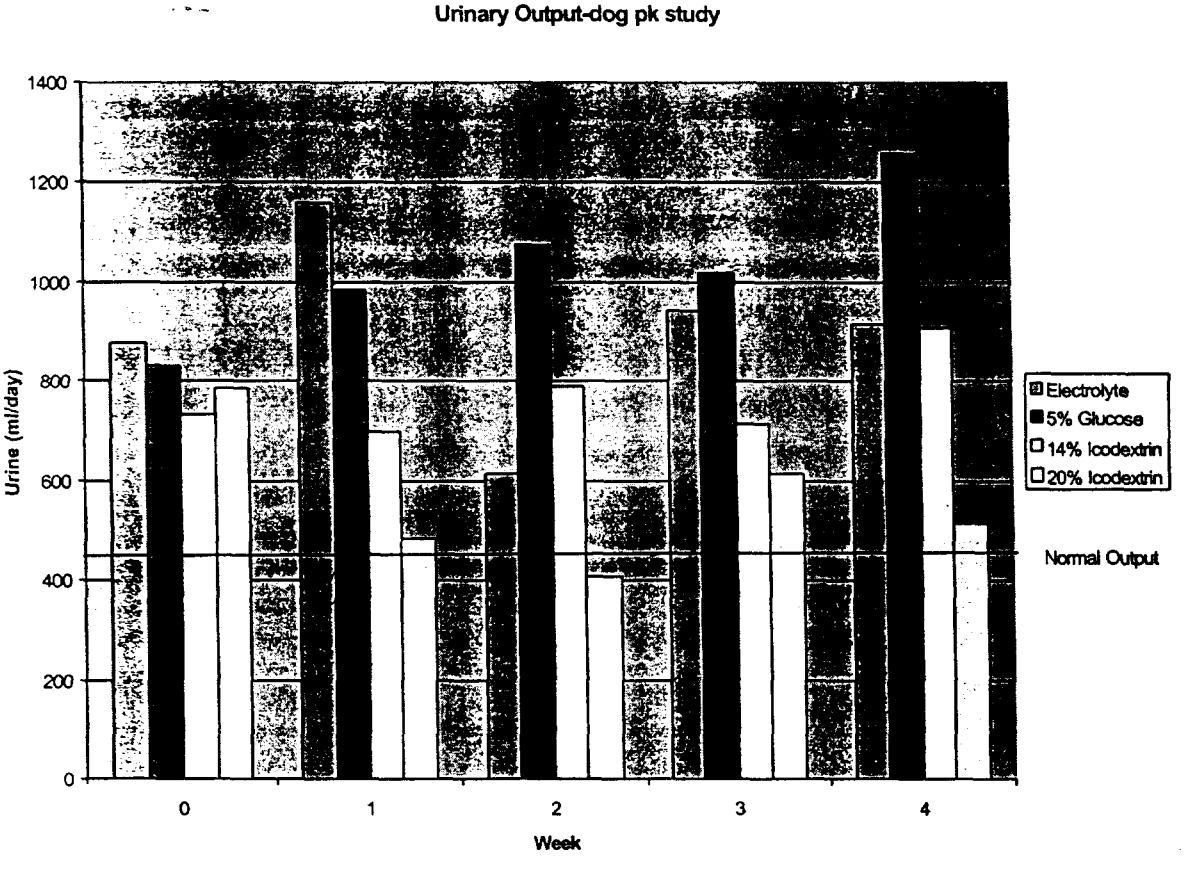
REPORT ON THE PHARMACOKINETIC STUDIES OF DEXTRIN 20 IN THE DOG

Basically, this study consists of blood and urine samples collected from the beagles used in the 28 day toxicity study and receiving 20% icodextrin solution. Samples were collected on Days 1,7,14, 21, and 28.

Blood samples were collected prior to the first daily instillation of the icodextrin solution, then 1, 2, 5, and 10 hours post first daily instillation. The final sample was collected at 24 hours, just prior to the next day's first instillation. Urine samples were collected over 24 hours by housing the beagle in a metabolism collection unit. The total volume was measured and a 10 ml aliquot was retained for testing.

In this study, 2 conclusions are arrived at: 1) that icodextrin dramatically reduces urinary output in healthy dogs over controls, and 2) that a large portion of the icodextrin is absorbed through the peritoneum in a gender specific manner. The issue of urinary output in this situation is of some interest,

however, the significance is unknown since these solutions are for a renal compromised population. Reduction of urinary output may be beneficial in this population.



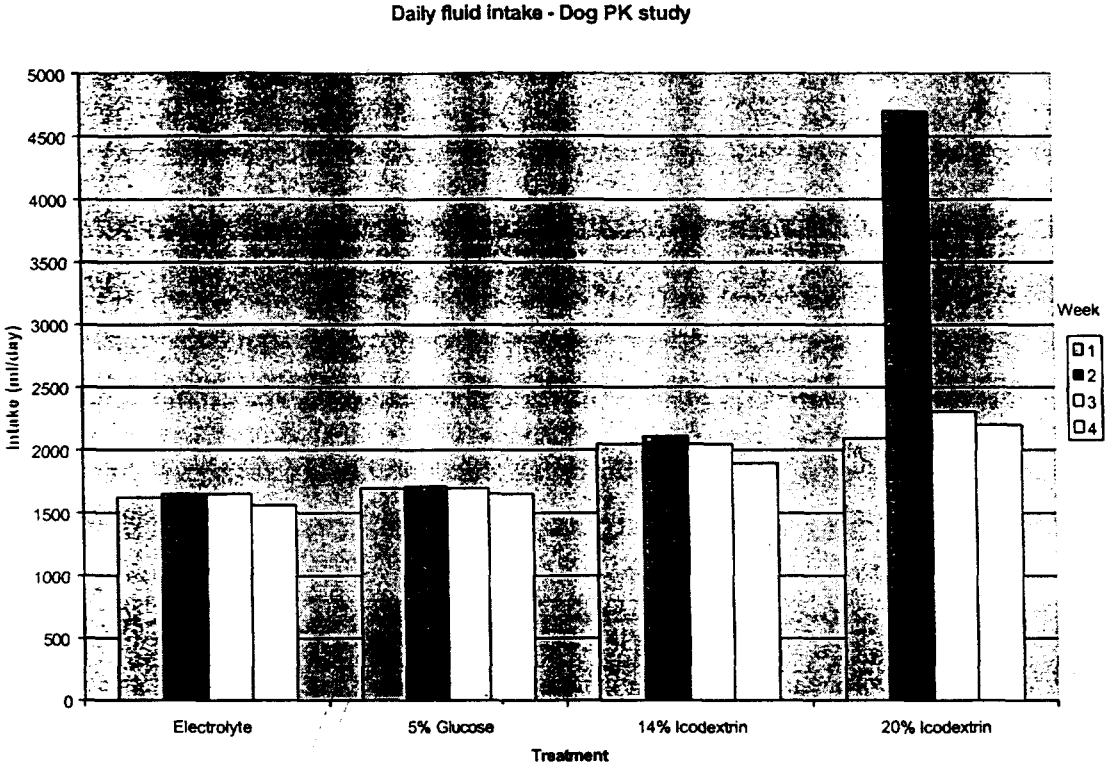


Figure _. Fluid intakes in the dog in the PK study.

Of more therapeutic difference are the gender differences in pharmacokinetics. The male and female dogs in the icodextrin treated groups maintain approximately equal levels of urinary output. However, male dogs excrete approximately 50% of the carbohydrate dose received in the peritoneal cavity, while the female dogs excrete approximately 30% of the carbohydrate dose received in the peritoneal cavity.

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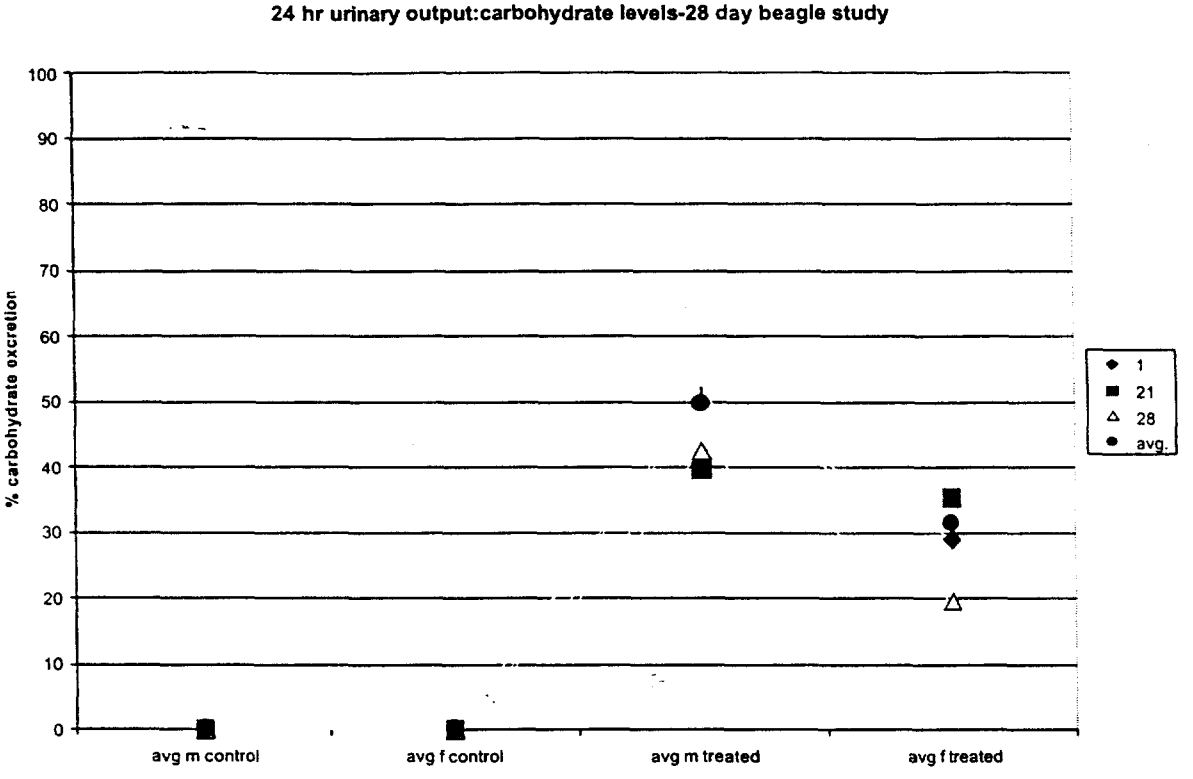

Figure _. Urinary carbohydrate output in dogs. PK study
Plasma carbohydrate levels followed a similar pattern, reaching higher peak levels in the male beagles than the female beagles. The difference in peak plasma carbohydrate levels after subtracting the pre-dose plasma carbohydrate levels was about 22%, similar to the difference in carbohydrate excretion by the dogs in the study.

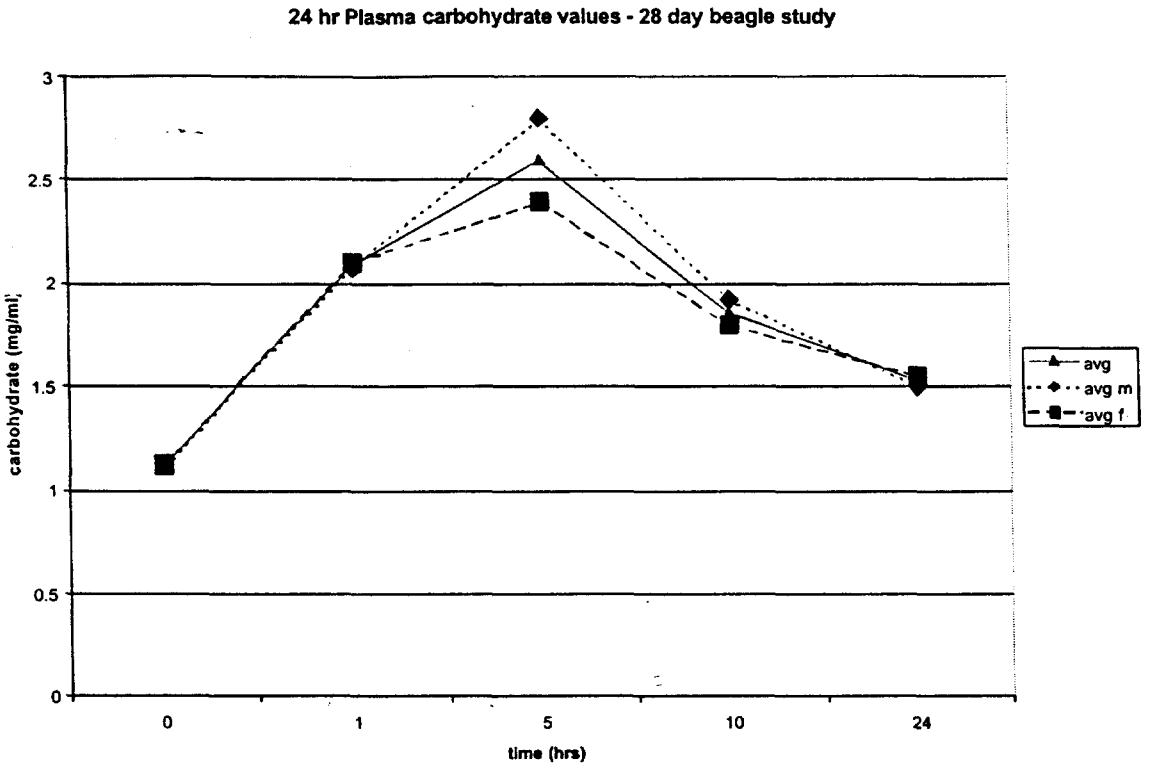

Figure _. 24 hr plasma carbohydrate levels from dogs. PK study
Also, of note is that the 14% and 20 % icodextrin dosages do increase blood glucose levels in the dogs. In fact, the icodextrin elevates blood glucose more than the 5% glucose dialysis solution. These studies are utilizing approximately 1.87 and 2.67 x the proposed level for usage in dialysis, which is 7.5%, and glucose is generally used at a 2.27% level, with 5% being 2.2 fold higher.

Fluid balance is an area of concern. One would anticipate that the animals receiving 20% icodextrin could potentially dehydrate. Urinary ourput is decreased in these animals relative to the controls, however, an increase in the levels of peritoneal dialysis fluid occurs, nearly doubling in some cases and largely offsetting the decreased urine output. However, although these two factors apparently offset each other, there is an increase in oral fluid intake. Apparently, with the electrolyte solution and 5% Glucose treatment, most of the fluid is absorbed from the peritoneal cavity, since ver little fluid is withdrawn. With the 20% glucose, the amount of fluid in the peritoneum increases, however, this is offset by an increase in drinking and decreased urination over the controls. Of note, by the end of the 28 day study, the 20% icodextrin group increased the level of peritoneal fluid recovery.

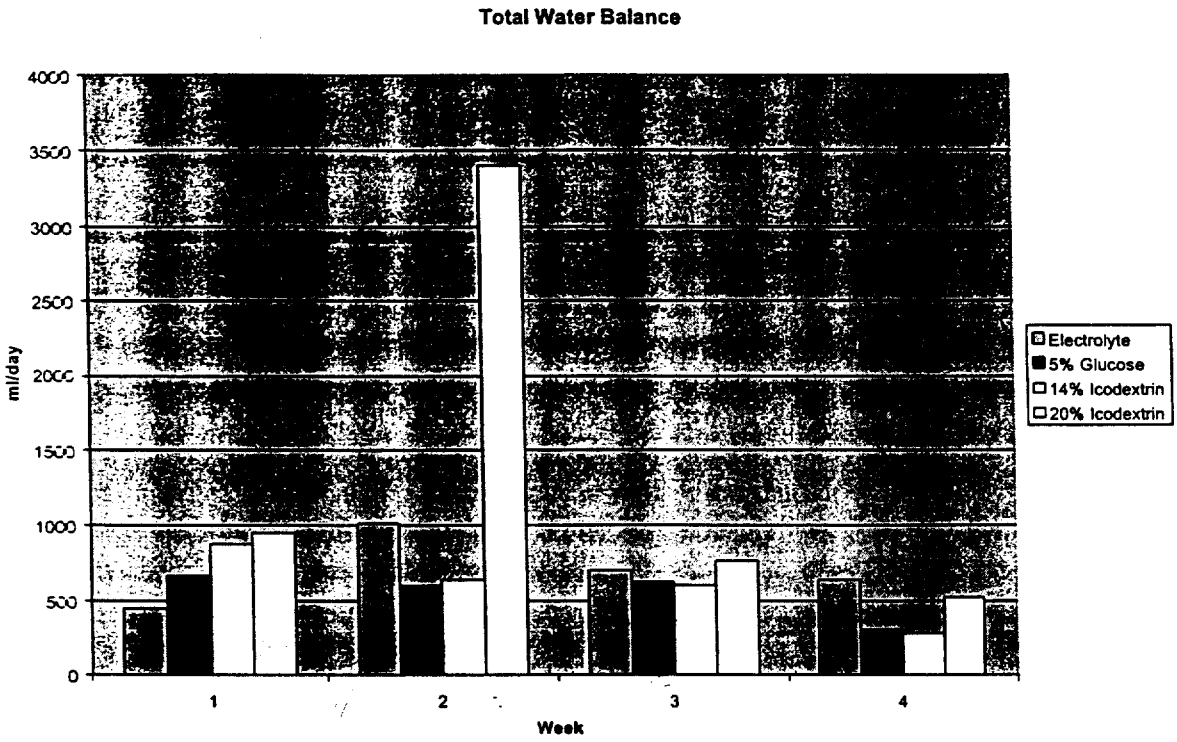

Figure _. Water balance in dogs. PK study

PK parameters: Standard pharmacokinetic parameters were not gathered in consideration of the intended usage of the drug substance.

Absorption: The icodextrin is presented in the peritoneal cavity and absorbed presumably through the mesenteric lymph node. The sponsor declined to use radio-labeled compounds to assess ADME. In the rat pharmacokinetic system, the icodextrin solution was injected intraperitoneally. Since there was no fluid withdrawl, all the icodextrin solution was absorbed. Serum and peritoneal amylases are the likely candidate enzymes for breaking down the icodextrin. Various size dextran chains were detected in the serum and urine, and overall, plasma carbohydrate and glucose levels were elevated in the presence of intraperitoneal icodextrin solution. With the anephric rat study, only 10% of the carbohydrate remained in the abdominal fluid after 8 hours, and an increase in glucose in the abdominal fluid equal to 0.67% of the initial carbohydrate dose. Plasma levels of carbohydrate accounted for another 5.3% of the original icodextrin dose, with another 3% accounted for by the increase in serum glucose over the controls. In the dogs, results showed male dogs absorbed more carbohydrate than females, however the study was not conducted in a manner that would allow for an accurate estimation of carbohydrate absorption for the dog.

Distribution: Without radiolabeling, it can be difficult to determine the source of the glucose throughout the body. Intraperitoneal icodextrin was absorbed and led to elevated plasma and urinary carbohydrate. Although not seen in the rat, in dogs the icodextrin treatment led to a prolonged increase

in serum glucose levels. Another sequelae of icodextrin treatment is an apparent increase in glycogen deposition, primarily in the liver, and intermittently found in the spleen and mesenteric lymph nodes. The glycogen deposition was not seen in the short term, anephric rat distribution study (8 hours), but was seen in the longer term (28 day) rat toxicity studies. In the anephric rat study, only ~20% of the carbohydrate could be accounted for, the disposition of the rest of the carbohydrate may be metabolic.

Metabolism: Icodextrin is a dextran polymer of approximately 12,000 to 20,000 daltons (glucose monomers are 180 daltons). The structure of icodextrin is virtually identical to that of glycogen, which the body has enzymes to breakdown. Serum amylases break the glucosidic $\alpha(1\text{-}4)$ linkages, while glycosidases break the branching glucosidic $\alpha(1\text{-}6)$ linkages. Once the icodextrin is broken down, it is metabolized as glucose. Since none of the drug substance was labeled, it is not possible to tell whether the glucose from icodextrin was more likely to be metabolized by the body or excreted. However, from the anephric rat study, it is possible that the majority of icodextrin absorbed is broken down to glucose and metabolized (~80% in the anephric rat study). The amount of carbohydrate remaining unaccounted for is approximately 2.7 kcal for a 125 g rat. Since the nutritional requirements for this size, young, growing rat are approximately 20 kcal/day, the 2.7 kcal could easily be metabolized.

Excretion: In rats, females after 28 days of treatment with 20% icodextrin solution were excreting approximately 25% of the received dose as carbohydrate, males 16%. With the 14% icodextrin, female rats excreted 14% and males 5%.
In dogs, females after 28 days of treatment with 20% icodextrin solution were excreting approximately 19.6% of the carbohydrate dose given, males 42%.
This data points out that there are gender specific issues in the way the icodextrin solution is handled in animals.
The opposite trends in the rats and dogs may be due to the very different structure of the studies. In the dogs, a semi-permanent catheter was placed and the study was conducted much as a peritoneal dialysis with 2 exchanges per day. In the rats, the solutions were injected into the peritoneum and fluid recovery was only attempted intermittently, and generally unsuccessfully.

Other studies: anephric rat distribution

Study title: Preliminary study for distribution of icodextrin in rats and Distribution of Icodextrin in Rats

Key study findings:

Study no: 10-1124 and 10-890
Volume #, and page #: Vol. 11, pp.169-190 and 191-213
Conducting laboratory and location: [redacted]
Date of study initiation: 12/12/1997
GLP compliance:
QA report: yes ( ) no (X)
Drug, lot #, radiolabel, and % purity: 15% Icodextrin, lot # BLID-98-07, ~97% pure
Formulation/vehicle:

Icodextrin	% w/v
Sodium Lactate	% w/v
Chloride (as NaCl)	% w/v
Calcium Chloride	% w/v
Magnesium Chloride	% w/v
Sodium	

Methods (unique aspects):

Species/strain: Sprague-Dawley Rats, CD
#/sex/group or time point (main study): 5 males, 5 weeks old
Age: 5 weeks
Weight: 115.5-137.1 g
Doses in administered units: 40 ml/kg
Route, form, volume, and infusion rate: intraperitoneal injection.

Assuming a 125 g rat, 5 ml of solution was given peritoneally, and 750 mg of icodextrin was given per animal for 150 g/L of total carbohydrate. Since 15.65 g/l are left in the peritoneum after 8 hours, ~90% is absorbed. 8g/L is still in the plasma after 8 hrs. Additionally, the plasma glucose levels are 4 fold elevated in the rats receiving icodextrin, accounting for ~6g/l of carbohydrate. In additon, 2.5 g of glucose is now found in the abdominal fluid, compared to 1.5 g in controls. All told, about 20% of the carbohydrate can be accounted for by addition. Rats of this size use about 20 kcal/day, and the remaining carbohydrate, would provide approximately 2.7 kcal (glucose yields 4.5 kcal/g) , therefore it could be metabolized by the rat. Unfortunately, only use of labeled glucose could provide a definitive answer.

Observations and times:

Clinical signs: tachypnea in most of the animals
Body weights: Electrolyte group 133.9 +/- 2.4 g, 15% icodextrin 128.7 +/- 2.1 g
Organs weighed: Liver and spleen
Other: abdominal fluid and plasma carbohydrates

Results:

Mortality: 2 of 9 from the electrolyte group and 2 of 9 from the 15% icodextrin group.
Clinical signs: prone position & tachypnea.
Body weights: No significant differences found
Organ weights: no significant differences found

Evaluation: icodextrin is readily absorbed from the peritoneal cavity in the rat. Within 8 hours of a 40 ml/kg dose of 15% icodextrin, 6 g/kg (human dose: 30 ml/kg of 7.5% icodextrin, 2.25g/kg), 90% of the dose was absorbed and approximately 5.3% was resident in the plasma. Another 5% of the dose was most likely the elevated glucose levels in the plasma (4 fold over controls) and the glucose levels in the abdominal fluid (67% over controls).

PK/TK summary: In summary, icodextrin is readily absorbed from the peritoneal cavity and is readily broken down into glucose monomers. Icodextrin is probably implicated in an increase in glycogen depostion in the liver. The results also show gender specific differences in 2 species with regard to excretion of the breakdown products of icodextrin and possibly absorption. The toxicities seen may be more related to the vehicle than the actual drug agent. However, since the drug agent is in the vehicle, it must be considered for toxicological purposes.

PK/TK conclusions: The studies utilized for pharmacokinetics display gender specific differences in excretion which are potentially related to metabolism. Rats have been well studied with regard to differences in energy metabolism, with female rats largely drawing on fat storage for energy, while male rats rely on glycogen stores to a much larger degree.

Briefly, male dogs absorb more carbohydrate from the peritoneum and also excrete a higher percentage of the absorbed dosage than female dogs. The treatments all induced polydipsia and polyuria in the animals. All animals maintained a positive water balance and signs of edema and swelling were commonplace.

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