

## Minutes of Telephone Conference Call between Baxter and the FDA

Date: November 9, 2001  
Application: NDA 21-321  
Extraneal (icodextrin) Peritoneal Dialysis Solution  
Sponsor: Baxter Healthcare Corporation  
Subject: Discussion of Labeling Issues

### FDA Participants

Robert Temple, M.D., Director, Office of Drug Evaluation I, HFD-101  
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110  
Douglas Throckmorton, M.D., Deputy Division Director, HFD-110  
Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110  
John Lawrence, Ph.D., Statistician, HFD-710  
Albert DeFelice, Ph.D., Pharmacology Team Leader, HFD-110  
James Willard, Ph.D., Pharmacologist, HFD-110  
Kasturi Srinivasachar, Ph.D., Chemistry Team Leader, HFD-810  
Ram Mittal, Ph.D., Chemist, HFD-810  
Natalia Morgenstern, Chief, Project Management Staff, HFD-110  
Andrew Haffer, Pharm.D., Regulatory Review Officer, DDMAC, HFD-42  
Cindy Kortepeter, Pharm.D., Safety Evaluator, DDRE I, OPDRA, HFD-430  
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

### Baxter Healthcare Corporation

Richard Newman, Ph.D., Vice President, Regulatory Affairs  
Marsha Wolfson, M.D., Vice President, Global Clinical Affairs

### **Background**

Extraneal (icodextrin) Peritoneal Dialysis Solution is proposed for the management of chronic renal failure. On October 22, 2001, the Agency issued an approvable letter with marked-up labeling for this New Drug Application (NDA). In an October 30, 2001 submission, Baxter submitted revised draft labeling based on their proposed changes and the changes recommended in the marked-up labeling enclosed with the approvable letter. On November 7, 2001, per the sponsor's request, Dr. Temple's comments on the October 30, 2001 draft labeling were faxed to Baxter. This teleconference was scheduled to discuss the labeling changes.

### **Teleconference**

The following changes to the proposed labeling dated October 30, 2001 were discussed:

### Non-proprietary Name

The Agency requested the deletion of "7.5%" before the drug name "icodextrin" because the weight-in-volume percentage is not part of the non-proprietary name. This change should be made globally to the package insert, patient package insert, and carton and container labeling. Also, "less than 10%" should be inserted before "alpha (1-6) glucosidic bonds" in the second sentence of the **DESCRIPTION** section.

### Clinical Studies

On page three of the draft labeling under **CLINICAL PHARMACOLOGY/Clinical Studies**, the Agency recommended deletion of the proposed statement ' \_\_\_\_\_

\_\_\_\_\_ because it was already included in the previous paragraph and represented in the figures. The sponsor felt that the inclusion of this statement was important in guiding patient therapy. However, Dr. Throckmorton commented that the proposed language was potentially confusing, as the more relevant dextrose solution was 4.25% dextrose. In addition, language regarding information for use should not be included in the **Clinical Studies** subsection.

The Agency recommended that the sponsor add the statement "There is no information on how creatinine and urea nitrogen clearances on Extraneal compare with 4.25% dextrose" since this comparison was not made in the studies.

### Serum Electrolytes

On page six under **PRECAUTIONS/Laboratory Tests/Serum Electrolytes**, the Agency asked for clarification of the proposed statement ' \_\_\_\_\_

\_\_\_\_\_ The sponsor explained that "the greatest mean decrease" referred to the largest decrease at any time point. Dr. Throckmorton noted that was inadequate, as it does not describe the extreme changes. He asked whether the sponsor could provide the average change from baseline or the maximum change from baseline in an individual. The sponsor pointed out that some patients who had a change greater than 5 mEq/L also had concomitant conditions, such as severe peritonitis. The Agency asked the sponsor to provide additional documentation for the language proposed in this section.

Other changes, including minor editorial and format changes, were conveyed to the sponsor.

### **Conclusion**

The language for the draft labeling, which incorporates the changes requested by the Agency, is attached. The sponsor was asked to submit their proposed language on the **CLINICAL PHARMACOLOGY/Clinical Studies** and **PRECAUTIONS/Laboratory Tests/Serum Electrolytes** subsections of the package insert by November 13, 2001. The Agency will follow up with the sponsor upon receipt of the proposed language.

Minutes Preparation:

Quynh Nguyen, Pharm.D.

11-29-01

Concurrence, Chair:

Robert Temple, M.D.

qn/11-26-01/11-27-01/11-29-01

rd: RTemple/11-29-01  
DThrockmorton/11-27-01  
NStockbridge/ 11-27-01  
JLawrence/11-26-01  
RMittal/11-27-01  
KSrinivasachar/11-27-01  
JWillard/11-26-01  
ADeFelice/11-27-01  
NMorgenstern/  
AHaffer/11-27-01  
CKortepeter/11-27-01

cc: NDA 21-321  
HFD-110  
HFD-110/QNguyen  
HFD-110/SMatthews

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

**Teleconference Meeting Minutes**  
**NDA 21-321**  
**Extraneal (7.5 % icodextrin)**  
**Peritoneal Dialysis Solution**

**Meeting Date:**

September 13, 2001

**FDA Attendees:**

Ramsharan Mittal, PhD., Review Chemist  
Kasturi Srinivasachar, PhD, Team Leader

**Baxter Healthcare Corporation Attendees:**

Joe Fosco, PhD, Sr. Manager, Product Development/Stability Operations  
Michael Koberda, PhD, Sr. Research Scientist  
Joe Giertych, PhD, Manager  
Mary Kay Rybicki, Assoc. Dir. Regulatory Affairs

**Background and Purpose of Meeting:**

This teleconference was requested by Baxter to obtain agreement with the Division for requirements for adequate responses to the CMC Information Request Letter dated September 7, 2001.

**Minutes:**

Baxter agreed to include % Mass in Range (Molecular Weight Distribution) in the drug substance – icodextrin- specifications and will modify icodextrin Mw (weight average) range as amended in DMF [redacted]

[redacted] will not be included as regulatory specifications and will not be monitored on routine stability due to extensive data and manufacturing experience with these containers- which demonstrate that these are consistently present only at very low levels. Baxter will provide a justification for not performing additional testing of [redacted] extractables.

Baxter will provide an explanation and justification, based upon studies for suitability, for not monitoring [redacted] as an extractable.

Baxter will provide the explanation that [redacted] is not an extractable, but rather a potential contaminant of the salts and icodextrin and that [redacted] is controlled in the raw materials. Baxter will not make [redacted] regulatory specification, but will establish a monitoring limit and test, at release, the first three production batches. The need for continued testing will be made in consult with the Division.

Baxter will add % Mass range to Mw and Mn as a regulatory specification. Baxter will provide an explanation that the combination of [redacted]

\_\_\_\_\_ determination provide specific identification of icodextrin  
Extraneal.

Baxter will provide the requested explanation of the validation for \_\_\_\_\_  
and support for assay ruggedness.

Baxter will provide an explanation supporting validation of the \_\_\_\_\_ assay, based  
upon: the validation of the assay for API by ML Laboratories; the method  
transfers from ML to Baxter, Round Lake, IL and from Baxter Round Lake to  
Baxter, Marion NC; and the validation for the \_\_\_\_\_ assay performed for a  
potential alternative API supplier.

Baxter agreed to try provide this information by the end of next week (9/21/01)  
and will contact Dr. Mittal if any delays are anticipated.

APPEARS THIS WAY  
ON ORIGINAL

## Meeting Minutes

**Meeting Date:** February 6, 2001  
**Sponsor:** Baxter Healthcare Corporation  
**Drug:** Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution  
**Subject:** Filing Meeting for NDA 21-321  
**Meeting Chair:** Raymond Lipicky, MD  
**Meeting Recorder:** John Guzman  
**Participants:**

### Attendees

Raymond Lipicky, MD	Director, Division of Cardio Renal Drug Products HFD-110
Stephen Fredd, MD	Deputy Director, HFD-110
Norman Stockbridge, MD, PhD	Team Leader, Medical, HFD-110
Jorge Rios, MD	Medical Officer, DSI, HFD-47
Emmanuel Fadiran, PhD	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Albert DeFelice, PhD	Team Leader, Pharmacology, HFD-110
Kasturi Srinivasachar, PhD	Team Leader, Division of New Drug Chemistry I, HFD-810
Ram Mittal, PhD	Chemist, Division of New Drug Chemistry I, HFD-110
James Hung, PhD	Team Leader, Statistical, Division of Biometrics I, HFD-710
John Lawrence, PhD	Statistician, HFD-710
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Sandra Birdsong	Regulatory Health Project Manager, HFD-110
John Guzman	Regulatory Health Project Manager, HFD-110

### **Background**

Baxter Healthcare Corporation has submitted Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution (NDA 21-321) for the long dwell exchange in peritoneal dialysis for the treatment of chronic renal failure. The related IND is  and has been designated an Orphan Drug (Designation No. 97-1056).

On October 4, 2000, a pre-NDA meeting was conducted to discuss the format of the NDA submission. Meeting Minutes are attached. On October 19, 2000 and closed-door Advisory Committee meeting was held to discuss the development of peritoneal dialysis solutions.

### **Meeting**

Below is a table identifying the review discipline and the estimated date of review completion:

<u>Discipline</u>	<u>Reviewer</u>	<u>Estimated Date of Review Completion</u>
Medical	Stephen Fredd, MD	First Week of June
Secondary Medical	Norman Stockbridge MD, PhD	TBA
Biostatistics	John Lawrence, PhD	First Week of June
Chemistry	Ram Mittal, PhD	Middle to End of June
Pharmacology	James Willard, PhD	First Week of June
Biopharmaceutics	Emmanuel Fadiran, PhD	First Week of June
Microbiology	Vivian Greenman, PhD	TBA
DSI	Jorge Rios, MD	TBA
Project Management	John Guzman	

**Other notes:**

- Drs Lipicky, Fredd, and Rios agreed that one of phase 3 studies should be inspected. The targeted study to be inspected was the phase 3 mortality protocol (Protocol RD-97-CA-131). A copy of that protocol will be sent to Dr. Rios.
- A methods validation package will be requested.
- Inspection of the manufacturing plants (both foreign and domestic) will be scheduled.
- This drug could be presented at the August 2001 Advisory Committee.

Signature, Meeting Recorder:

John Guzman

Signature, Meeting Chair:

Raymond Lipicky, MD

Drafted: February 22, 2001

Cc: orig NDA 21-321  
HFD-110  
HFD-110/Guzman

Rd: Lawrence 23-Feb-01  
Hung 02-Mar-01  
Mittal 02-Mar-01  
Srinivasachar 02-Mar-01  
DeFelice 02-Mar-01  
Fadiran 05-Mar-01  
Stockbridge 02-Mar-01  
Fredd 06-Mar-01

/s/

-----  
John Guzman  
3/7/01 03:24:45 PM  
Filing Meeting Minutes

Raymond Lipicky  
3/7/01 03:49:27 PM

J.F.  
DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION

OCT 10 2000



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
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Rockville, MD 20852

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Transmitted to FAX Number: 847-473-6952  
Attention: Mr. Steven I. Engel, M.S., Pharm.D.  
Company Name: Baxter Healthcare Corp.  
Phone: 847-473-6558  
Subject: October 4, 2000 Meeting Minutes  
Date: 10/10/00  
Pages including this sheet: 4  
From: Sandy Birdsong  
Phone: 301-594-5312  
Fax: 301-594-5494

Dear Steve,

The minutes from our October 4, 2000 meeting regarding IND [redacted] (Extraneal) accompany this cover sheet.

**You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).**

Please let me know you received this facsimile. Thanks!

cc: orig  
HFD-110  
HFD-110/Birdsong

Pre-NDA Meeting  
IND [redacted]  
(NDA 21-321)

OCT 10 2000

Date: October 4, 2000  
Application: Extraneal (icodextrin)  
IND [redacted]  
Sponsor: Baxter Healthcare  
Date of Receipt: September 20, 2000  
Meeting Confirmation: September 22, 2000  
Indication: Peritoneal Dialysis  
Classification: B  
Purpose of Meeting: Pre-NDA Meeting

**Participants:**

**FDA**

Raymond Lipicky, Director, Division of Cardio-Renal Drug Products, HFD-110  
Douglas Throckmorton, M.D., Deputy Director, HFD-110  
Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110  
Juan Carlos Pelayo, M.D., Medical Officer, HFD-110  
James Hung, Ph.D., Statistician, Division of Biometrics I, HFD-710  
Timothy Link, Ph.D., Pharmacologist, HFD-110 (Pre-Meeting only)  
Sandra Birdsong, Regulatory Health Project Manager, HFD-110  
Gabriel Robbie, Ph.D., Clinical Pharmacologist/Biopharmaceutist, HFD-860 (Pre-Meeting only)  
Albert DeFelice, Ph.D., Pharmacology Supervisor, HFD-110 (Pre-Meeting only)

**Baxter**

James Moberly, Ph.D., Director, Research and Development  
Marsha Wolfson, M.D., Medical Director  
Steven B. Engel, Ph.D., Vice President, Regulatory Affairs  
Mary Kay Rybicki, Associate Director, Regulatory Affairs  
Angela Gordon, Ph.D., Global Project Director  
Frank Ogrinc, Ph.D., Senior Research Scientist, Clinical Statistics  
Robin Reynolds, Manager, Clinical Affairs

**Meeting**

The Division Director stated the purpose of this meeting is to discuss the format of the data. A secondary goal is to discuss the upcoming closed session of the Advisory Committee on October 19, 2000.

The Division itemized the format of the NDA data submission as follows:

- Annotated case report forms with the SAS variable for every protocol and SAS transport file with those variables at each entry. Case report forms should be submitted as PDF files for the review.
- A relatively short report on analysis of the data. It isn't necessary to have an integrated summary of efficacy. The report need not be lengthy. The data is the driving force.
- The protocols with their amendments, giving a chronology of the changes. Tabular listings are not needed. The sponsor may present whatever they wish.
- If literature is cited, it is helpful to have reprints as part of the NDA.
- Case report forms for deaths and dropouts, and how dropouts are handled. A narrative summary of each death and dropout is needed.
- A standard Chemistry Section.
- A pharmacology section explaining why chronic animal toxicology isn't needed.
- The report should be on paper, but it can be on CD ROM. as well. For the purposes of this NDA, a paper submission is still permissible.

The sponsor presented the Table of Contents of the NDA submission to facilitate identification of items that are required for this submission. These items are as follows:

- Clinical Data. The Division does not require an overview, but it is acceptable to have one.
- Clinical Pharmacology, which should be submitted in standard format.
- Controlled Clinical trials. The Division recommends inclusion of a Table, but a Synopsis is not necessary.
- Clinical Study Reports. Data listings and a list of investigators are not necessary. Annotated case report forms for each study, the analyses performed by study, and a synopsis of the report. The sponsor stated that there is an analysis of the report for each case report form module and the FDA statistician stated this is acceptable.
- Ongoing studies should be in the form of a Table. The Division stated that once the sponsor has looked at the data and has decided how to analyze the data, they should proceed; the Division cannot specify what analyses should be done.
- Marketing experience and foreign regulatory actions should be communicated.
- An Integrated Summary of Safety is required, but a lengthy one is not required.
- An Integrated Summary of Efficacy is required. A risk-benefit analysis is not necessary. The FDA Statistician asked the company to submit the SAS codes for their analyses.
- In terms of Adverse Events, the sponsor plans a cutoff of 5% of total incidents. The Division suggested that a Table giving the difference between drug and control. The Division noted that questions arise when the data analysis of the sponsor and the Division do not coincide. The Division requested that the sponsor supply the SAS code.

#### **Advisory Committee**

The Division reviewed the current plans for the October 19, 2000 Closed Advisory Committee session with the sponsor. The questions for the Committee have not been written. The Project Manager

will send the draft questions as soon as they are available, and will send a list of the attendees, as well. The Agenda is identical to that in the sponsor's briefing book. All Committee members have received a copy of the sponsor's briefing package.

Although the Agenda indicates that the meeting will be held in Conference Room F, Woodmont II Office Complex, this room cannot accommodate all of the participants. The meeting will be held in the Jack Mazur Auditorium at The National Institutes of Health, Bethesda, MD.

The Division suggested that the sponsor contact Dr. John Tracy of Advisory Committee Management, to ask if there are specific rules regarding recording of the proceedings by the sponsor. The sponsor should also contact the Executive Secretary, Joan Standaert, regarding audio/visual needs for their presentation. Although slides need not be submitted in advance, the Division suggested that the sponsor provide approximately 30 copies of their slides.

The sponsor's list of questions will be addressed at the meeting. Dr. Lipicky outlined the thinking process of the Committee and the type and pattern of questions from the Committee. The key questions are, what are the greatest concerns? Dr. Lipicky emphasized that there aren't many rules, other than each speaker must be recognized by Dr. Milton Packer, Chair.

The sponsor stated they are moving forward

Dr. Lipicky suggested that the sponsor proceed with submission of their NDA after the October Advisory Committee. The Division recommended there be a meeting with the sponsor at the end of January, after the application is received.

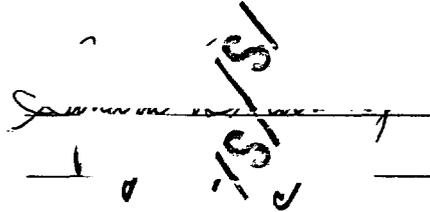
Dr. Lipicky indicated that the decision level for this application has not been made at this time.

#### Conclusion

- The draft of the Division's questions for the Advisory Committee will be available by the end of next week. The Project Manager will send them to the sponsor as soon as they are available.
- The Project Manager will send the list of Advisory Committee members to the sponsor.
- The sponsor will contact the Advisory Committee Executive Secretary (Joan Standaert) to see what equipment is provided by NIH and what the sponsor should bring.
- The sponsor will contact Advisory Committee Management (Dr. John Tracy) regarding any regulations about recording the meeting.

Signature, Meeting Recorder

Concurrence, Chair



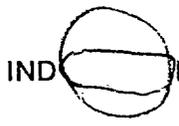
RD: Pelayo/10/5/00  
Hung/10/5/00  
Link/10/6/00  
Stockbridge/10/6/00  
Throckmorton/10/6/00

Final: slb/10/10/Q0\_

Cc:  
HFD-110  
HFD-110/S. Birdsong  
HFD-110/S. Matthews

DF

AUG 12 1997



Minutes

August 6, 1997

IND Extraneal (with 7.5% Icodextrin) Peritoneal Dialysis Solution  
Baxter Healthcare Corporation, Renal Division  
End-of-Phase 2 Meeting

Related submissions: July 30, 1997

Attending:

Baxter:

Richard Newman, Ph.D.	Vice President, Global Regulatory and Clinical Affairs
Marsha Wolfson, M.D.	Medical Director, Global Clinical Affairs
Leo Martis, Ph.D.	Vice President, Solutions Development
Angela Gordon, Ph.D.	Team Leader, Extraneal Project
Frank Ogrinc, Ph.D.	Statistician, Applied Sciences, Corporate Research
Steven Hoff, Ph.D.	Manager, Regulatory Affairs

FDA:

Robert Temple, M.D.	HFD-101	Office Director/Chair
Shaw Chen, M.D., Ph.D.	HFD-110	Group Leader/Medical
Juan Carlos Pelayo, M.D.	HFD-110	Medical Officer
Lu Cui, Ph.D.	HFD-710	Statistician
Donald Haggerty, M.D.	HF-35	Medical Officer, Office of Orphan Products Development
Gary Buehler	HFD-110	Regulatory Health Project Manager
Kathleen Bongiovanni	HFD-110	Regulatory Health Project Manager/ Minutes Recorder
Douglas Throckmorton, M.D.	HFD-110	Medical Officer
Isaac Hammond, M.D.	HFD-110	Medical Officer
Khin U, M.D.	HFD-110	Medical Officer

**Background:** Baxter had two previous meetings with the Division, on March 12 and April 30, 1997, to discuss the clinical development program for Extraneal Peritoneal Dialysis Solution. Dr. Temple was unable to attend these meetings. The firm did not agree with the recommendations that Dr. Lipicky made, so we offered them a meeting with Dr. Temple in attendance, and they accepted.

One study, MIDAS, has already been done, and the results were submitted to the IND. Baxter has proposed two additional studies: a one-month efficacy and safety study comparing Extraneal to Dianeal 2.5% dextrose solution, with at least 37 patients per arm; and a 12-month safety study, comparing Extraneal to Dianeal, with 150 patients total.

**Meeting:**

Meeting Objective (from pre-meeting submission):

Discussion of the clinical utility of the proposed protocols for the evaluation of Extraneal's safety and efficacy.

DISCUSSION POINTS

Purpose of the Trials

Baxter explained that Extraneal is meant to enhance long-dwell sustained ultrafiltration (8-16

hours). They believe that Extraneal use may allow a physician to manage patients better. Dr. Temple asked them how they could show advantages in relevant subpopulations. Baxter replied that they would prefer to show initially that they are as good as Dianeal, rather than trying to show superiority. Once they are on the market, they would then perform some focused trials. Dr. Temple reminded them that they cannot claim or imply any differences without adequate data, and there will not be much to say if they have only shown that they are an effective dialysis solution.

Dr. Temple said that they may have better access to patients if physicians knew they are looking for advantages over standard solutions. He asked whether they could show differences in glycosylated hemoglobin levels in patients with glucose intolerance, or improved nutritional status in patients who are malnourished. He suggested that they include subset hypotheses on these types of patients in their trials.

Baxter noted that they have had difficulty recruiting adequate numbers of malnourished patients in other trials. Dr. Temple said that they could begin these trials and submit efficacy supplements later.

#### Design of the Efficacy Trial

Dr. Temple suggested that they use a non-inferiority design in the efficacy trial, using measurements of patient weight, creatinine clearance, and other measures of effect to show that Extraneal is not worse than standard therapy for usual dialysis parameters by a pre-specified amount. He said that we are particularly interested in having them rule out any adverse effects on the peritoneal membrane. They might consider measuring the rate of membrane deterioration over time compared to control. Baxter said that both proposed studies include peritoneal equilibration testing (PET).

#### Numbers of Patients

Dr. Temple noted that the proposed number of patients that will have been treated with Extraneal is at the low end of what we would like to see, but the number necessary depends in part on the ability to detect differences between Extraneal and conventional solutions. If there were a significant advantage in the loss of ultrafiltration, the numbers proposed may be sufficient. There will be about 100 patients who have been exposed for one year or more, a borderline exposure where the adverse effects of concern are chronic ones. He said it would be helpful if they could provide study data from patients using the product in Europe, where it is now marketed, and that they include data from a European registry. He said that he would like to keep open the possibility of a registry in the U.S., depending on how much data are available pre-marketing.

Dr. Temple asked the firm to consider adding more patients to the 12-month trial, since a small trial may be more susceptible to trouble. Dr. Pelayo suggested a target of 150 patients per arm completing the trial. Dr. Temple suggested that they consider an unbalanced randomization in this case, with perhaps a 2:1 ratio of patients on Extraneal:Dianeal, to focus more on the safety of the test treatment.

The firm said that they will look at rates of survival in the 12-month study, but it is not an endpoint.

Baxter said that they will have an additional European controlled trial, with 40 patients total, by the time of NDA submission. Dr. Temple said that all additional patients will contribute.

#### European Trials

Baxter asked whether we would accept trials done in Europe to support claims. Dr. Temple

assured them that we will accept well done studies from anywhere.

### Proposed Indication

Dr. Temple asked the firm what data they had to support the statement from their proposed indication "Extraneal is recommended... particularly for patients who have lost ultrafiltration on glucose solutions, because it can extend time on [continuous ambulatory peritoneal dialysis] CAPD therapy in such patients." Baxter explained that statement was included in the European labeling, and it is based on uncontrolled compassionate use study data. They said that it is more difficult to get patients onto hemodialysis in Europe, and patients are kept on peritoneal dialysis longer. Physicians who thought that a patient was developing membrane failure could enroll patients in this study. Baxter showed an overhead (copy attached) that showed that about 30% of these patients were maintained on Extraneal for over 24 months. Dr. Pelayo noted that there is some spontaneous recovery from apparent membrane failure, so without a control group it is difficult to draw conclusions from the data. Dr. Temple suggested that they could perform a study on patients developing membrane failure randomized to Extraneal or conventional therapy. When patients failed, they would be withdrawn from the trial. This could be a very short duration trial that may provide persuasive data.

### Timing of Submissions

Baxter asked whether they could submit the results of the MIDAS trial, the one-month efficacy trial, and an interim report on the 12-month safety study in the original NDA submission, with the final report on the 12-month safety study to follow. Dr. Temple said that would be impossible if the NDA had a priority designation. He said that if it is a standard NDA, he would defer that decision to Dr. Lipicky.

### Product Improvements

Baxter asked whether it would be necessary to perform additional clinical trials when they propose to modify peritoneal dialysis solutions slightly, such as by changing the pH, to improve their quality. Dr. Temple said that since the main question is the effect on membrane function, and no one knows specifically why deterioration occurs, they would have to have clinical data showing no differences in membrane effects between product versions to support all changes except something like reducing contaminants.

### Absorption

Dr. Temple asked the firm to provide data about the consequences of absorbing maltose, polymaltose, and other metabolites/degradation products. Baxter said that blood levels rise for about 2 weeks and then level off to about 4 grams/L of glucose polymers and 1 gram/L of maltose. These levels return to baseline by 2 weeks after Extraneal is stopped. They have some animal studies, but these products are excreted by the kidney they do not have much data on nephrectomized animals. They said that some of these products are removed by the other exchange media used in the patients. They have not seen any apparent accumulation in the reticulo-endothelial system, but they have no long-term controlled studies.

### Minutes

We agreed to exchange meeting minutes with Baxter.

### Conclusions

- Dr. Temple reminded the firm that they cannot claim or imply any differences between Extraneal and other therapies without adequate data. Although not necessary, we suggested additional studies to examine effects on glycosylated hemoglobin in glucose

intolerant patients, on nutritional status in malnourished patients, and on ultrafiltration in patients developing membrane failure.

- Dr. Temple suggested that Baxter use a non-inferiority design in the efficacy trial, using measurements of patient weight, creatinine clearance, and other measures of effect to show that Extraneal is not worse than standard therapy by a pre-specified amount and to rule out any adverse effects on the peritoneal membrane.
- We encouraged the firm to increase the number of patients exposed to Extraneal, and to include data from European patients, including the available registry. Dr. Temple would like to keep open the possibility of a registry in the U.S. until after additional data are available.
- Dr. Lipicky will make the decision about the acceptability of submitting the final report on the 12-month study after the NDA is submitted.
- We will exchange minutes with Baxter.

Signature, minutes preparer:

*15/*  
\_\_\_\_\_  
Kathleen F. Bongiovanni

Concurrence Chair:

*15/* \_\_\_\_\_ *8/12/97*  
Robert Temple, M.D.

Attachment: copy of overhead

cc: IND                       
HFD-110  
HFD-101/RTemple  
HFD-111/KBongiovanni  
HFD-111/SBenton  
HFD-710/GChi

kb/8/8/97; 8/11/97; 8/12/97.

R/D: GBuehler/8/8/97; JCPelayo/8/8/97; LCui/8/8/97; SChen/8/11/97;  
RTemple/8/12/97.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

MEETING MINUTES

APR 9 1997

Date: March 12, 1997 1:30 PM CR "F" WOC II

Subj: End of Phase II Meeting  
IND [REDACTED] Extraneal (icodextrin 7.5%) PDS

Sponsor: Baxter Healthcare

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

Sponsor Lead: Steven Hoff, Ph.D.

Baxter Attendees:

Richard Newman, Ph.D.	VP, Global Regulatory and Clinical Affairs
Leo Martis, Ph.D.	VP, Solutions Development
Marsha Wolfson, M.D.	Medical Director, Global Clinical Affairs
Frank Ogrinc, Ph.D.	Statistician, Applied Sciences, Corporate Research
Steven Hoff, Ph.D.	Manager, Regulatory Affairs

FDA Attendees:

Raymond Lipicky, M.D.	Dir., Div of Cardio-Renal Drug Products, HFD-110
Shaw Chen, M.D., Ph.D.	Supervisory Medical Officer, HFD-110
Juan Carlos Pelayo, M.D.	Medical Reviewer, HFD-110
Lu Cui, Ph.D.	Statistician, HFD-710
Patrick Marroum, Ph.D.	Team Leader, Div. of Pharm. Eval. I, HFD-860
Gary Buehler	Project Manager, HFD-110
Isaac Hammond, M.D., Ph.D.	New Staff
Femi Williams, M.D.	New Staff
Khin U, M.D.	New Staff
Douglas Throckmorton, M.D.	New Staff
Steven Caras, M.D., Ph.D.	New Staff

**BACKGROUND**

Baxter submitted the IND for Extraneal on November 5, 1996. Their submission contained a protocol for a U.S. study comparing Extraneal to existing peritoneal dialysis solutions (Dianeal 2.5% and 4.25%) and the results of a completed open-label trial conducted in Europe. From the results of the European trial, the firm believed that Icodextrin would be more effective than the 2.5% Dianeal and equally effective to the 4.25%. It was the firm's intention to use these two trials to support an NDA for the product.

Dr. Pelayo reviewed the protocol for the proposed trial and his comments and suggestions were forwarded to the firm. They addressed the comments in their pre-meeting submission and planned to discuss them at the meeting.

## DISCUSSION POINTS

### Possible Labeling Claims

T

J

#### Safety

Dr. Lipicky said that the efficacy of the product has been shown in their European trial. The issue would be the safety. Dr. Pelayo said that they have not shown that the side effects of icodextrin are greater, the same, or less than conventional dialysis solutions. The firm replied that because of the low incidence of peritonitis, it would be difficult to impossible to show a difference in that event. Also, the rate of peritonitis is highly dependant on the technique used. With a population of about 30,000 patients total in the U.S., it would not be possible to address that issue.

The firm asked about post-marketing data from Europe. Would the AE reports be of value. Dr. Lipicky said that using an uncontrolled data base of that sort could get them into trouble. Basically any event that was reported would be attributed to icodextrin.

Dr. Lipicky said that the real question was what the incidence of unexpected serious events would be. To answer this question would take a trial of at least 1000 patients. Because this does not seem reasonable in light of the number of available patients, addressing the issue presents a problem. Dr. Lipicky said that we would have to discuss this problem internally and get back to the firm. He presented the following two possible outcomes:

1. The application could be approved on the basis of being Additional safety data would be required, but the type and amount remains to be determined.
2. A large definitive study would have to be completed that would define the safety profile of icodextrin. It was realized that this could be difficult to impossible to complete.

Dr. Chen suggested a post-marketing register. Dr. Lipicky said that because the patients cannot be randomized, the register may provide data that could shed a adverse light on the drug.

**CCPD vs. CAPD**

Dr. Pelayo asked why the firm is targeting patients using continuous cyclic peritoneal dialysis (CCPD) and not including patients on continuous ambulatory peritoneal dialysis (CAPD). The firm stated that, while there are far fewer patients on CCPD at this time, because of automated peritoneal dialysis machines allowing longer dwell times, it is becoming more popular. They have defined the use of icodextrin in CAPD patients in their European trial, and they wanted to do a study in CCPD patients to parallel today's trending therapy.

**ACTION ITEMS**

1. Because of the inability to provide definitive information regarding what trials would be required for approval of icodextrin, the firm was informed that the Division would get back to them with a decision. They were instructed to contact Mr. Buehler in about 1 week.

Minutes taken by:           / S /          

Gary Buehler

Concurrence, Chair:           / S /          

Raymond Lipicky, M.D.

Orig IND  
HFD-110  
HFD-110 GBuehler  
HFD-110 SBenton

RD: JCPelayo  
SChen  
LCUI  
PMarroum 3/27/97

**Integrated Summary of Safety (ISS)**

Please see the accompanying archival volumes 1.71 to 1.76 for the ISS.

**APPEARS THIS WAY  
ON ORIGINAL**

Integrated Summary of Effectiveness (ISE)

Please see the accompanying archival volumes 1.69 to 1.70 for the ISE.

**APPEARS THIS WAY  
ON ORIGINAL**

October 22, 2001

Marked-up

Draft Labeling

marked-up with - Dr. Temple's,

DDMAC and Pharmtox

reviewers' comments

for the Approvable letter.

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

## Locicero, Colleen L

---

**From:** Fortney, Russell  
**nt:** Friday, December 13, 2002 10:00 AM  
**Beam, Sammie**  
**Cc:** Throckmorton, Douglas C; Locicero, Colleen L  
**Subject:** RE: Extraneal (NDA 21-321)

Thanks Sammie. That makes things easier...

Russell

-----Original Message-----

**From:** Beam, Sammie  
**Sent:** Friday, December 13, 2002 9:56 AM  
**To:** Fortney, Russell  
**Subject:** RE: Extraneal (NDA 21-321)

Hi,

It is close enough if it is going to be approved in the next week or so. If it is delayed for more than a 2 to 3 weeks, maybe we should look at it again.

Sammie

-----Original Message-----

**From:** Fortney, Russell  
**Sent:** Friday, December 13, 2002 7:22 AM  
**To:** Beam, Sammie  
**Subject:** Extraneal (NDA 21-321)

Hi Sammie,

I took over for Quynh at Cardio-Renal and inherited this NDA.

I've been trying to get the approval letter out this week.....but got held up with a chemistry review. Because of that, we've gone past the 90 days for which your last tradename review was valid. Today is day 91. I didn't even realize this until after I dropped off the package at Dr. Temple's office (Colleen told me).

What should I do about this?

Thanks,

Russell

**MEMO**

**To:** Douglas Throckmorton, M.D.  
Director, Division of Cardio-Renal Drug Products  
HFD-110

**From:** Hye-Joo Kim, PharmD  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Through:** Alina Mahmud, RPh  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

Jerry Phillips, RPh  
Associate Director, Office of Drug Safety  
HFD-420

**CC:** Quynh Nguyen  
Project Manager  
HFD-110

**Date:** September 10, 2002

**Re:** ODS Consult 01-0135-3; Extraneal (7.5% Icodextrin); NDA 21-321

---

This memorandum is in response to a September 3, 2002 request from your Division for a re-review of the proprietary name, "Extraneal". "Extraneal" was found acceptable by ODS (formally known as OPDRA) on July 17, 2001 (ODS consult 01-0135), November 14, 2001 (ODS consult 01-0135-1), and February 27, 2002 (ODS consult 01-0135-2).

DMETS has not identified any safety concerns that would render the proposed name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Hye-Joo Kim  
9/12/02 10:14:48 AM  
PHARMACIST

Alina Mahmud  
9/12/02 10:25:28 AM  
PHARMACIST

Jerry Phillips  
9/12/02 05:40:34 PM  
DIRECTOR



**Memorandum**

**Date:** February 27, 2002

**To:** Douglas Throckmorton, M.D.  
Acting Director, Division of Cardio-Renal Drug Products  
HFD-110

**From:** Jennifer Fan, Pharm.D.  
Safety Evaluator, Office of Drug Safety  
HFD-400

**Through:** Carol Holquist, R.Ph.  
Deputy Director, Office of Drug Safety  
HFD-400

**CC:** Quynh Nguyen  
Project Manager, Division of Cardio-Renal Drug Products  
HFD-110

**Subject:** NDA 21-321, Extraneal (7.5% icodextrin), ODS Consult 01-0135-2

This memorandum is in response to a February 4, 2002 request from your Division for a re-review of the proprietary name, "Extraneal". "Extraneal" was found acceptable by ODS (formally known as OPDRA) on July 17, 2001 in the OPDRA consult 01-0135 and on November 14, 2001 in the OPDRA consult 01-0135-1.

DMETS has not identified any safety concerns that would render the proposed name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Jennifer Fan  
2/27 02 04:07:45 PM  
PHARMACIST

Carol Holquist  
2/27 02 04:14:11 PM  
PHARMACIST



DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service  
Food and Drug Administration

**Memorandum**

**Date:** November 14, 2001

**To:** Raymond Lipicky, M.D.  
Director, Division of Cardio-Renal Drug Products  
HFD-110

**From:** Jennifer Fan, Pharm.D.  
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment  
HFD-400

**Through:** Jerry Phillips, R.Ph.  
Associate Director, Office of Post-Marketing Drug Risk Assessment  
HFD-400

**CC:** Daryl Allis  
Project Manager, Division of Cardio-Renal Drug Products  
HFD-110

**Subject:** NDA 21-321, Extraneal (7.5% icodextrin), OPDRA Consult 01-0135-1

This memorandum is in response to a June 13, 2001 request from your Division for a re-review of the proprietary name, "Extraneal". "Extraneal" was found acceptable by OPDRA on July 17, 2001 in the OPDRA consult 01-0135.

OPDRA has not identified any safety concerns that would render the proposed name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the Medication Errors Project Manager, Sammie Beam, at 301-827-3231.

**APPEARS THIS WAY  
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Jennifer Fan  
11/16/01 10:25:15 AM  
PHARMACIST

Jerry Phillips  
11/16/01 02:21:48 PM  
DIRECTOR

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** 6/22/01

**DUE DATE:** 7/16/01

**OPDRA CONSULT #:** 01-0135

**TO:**

Raymond Lipicky, MD  
Director, Division Cardio-Renal Drug Products  
HFD-110

**THROUGH:**

Daryl Allis  
Project Manager  
HFD-110

**PRODUCT NAME:** Extraneal (7.5% icodextrin)

**MANUFACTURER:** Baxter Healthcare

**NDA:** 21-321

**SAFETY EVALUATOR:** David Diwa Pharm.D.

**SUMMARY:** In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA has performed a review of the proposed proprietary names Extraneal to determine the potential for confusion with marketed drug products and pending drug names.

**OPDRA RECOMMENDATION:** OPDRA has no objections to the use of the proprietary name Extraneal. In addition, we have recommended implementation of the labeling revisions to minimize potential user error.

**FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

**FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

**FOR PRIORITY 6 MONTH REVIEWS**

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/s/

/s/

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 07/11/01  
NDA: 21-321  
NAME OF DRUG: Extraneal (7.5% icodextrin)  
NDA HOLDER: Baxter Healthcare.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for an assessment of the proposed proprietary drug name Extraneal. The applicant Baxter Healthcare has proposed the name for 7.5% icodextrin peritoneal dialysis solution.

PRODUCT INFORMATION

Extraneal (7.5% icodextrin) is an isosmotic peritoneal dialysis solution containing icodextrin, a starch derived colloid osmotic agent. Each liter of Extraneal contains 75 grams of icodextrin in an electrolyte solution with 40 mEq/l lactate. The electrolytes maintain electrolyte balance and lactate normalizes acid-base status. The product is intended for single daily exchange intraperitoneal administrations with a recommended indwell time of 8 to 16 hours. Extraneal is indicated for a single daily exchange during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) in the management of chronic renal failure. It is contraindicated in patients with known cornstarch or icodextrin allergy. In addition, patients with glycogen storage disease should not receive this product. Insulin dependent diabetes patients may require modification of insulin dosage following initiation of therapy with Extraneal. The product contains no bacteriostatic or antimicrobial agents.

Extraneal solution may be warmed with dry heat to 37°C (98°F) prior to use and should be administered for 10-20 minutes. The product is packaged in polyvinyl chloride Ultra-Bag and Ambu-Flex III bag container systems. Each container system will be available in volumes of 1.5, 2 and 2.5 liters. The recommended storage temperature is 68-77 °F (20-25°C) in moisture barrier overwrap.

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research**

**II. RISK ASSESSMENT:**

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3,4</sup> as well as databases<sup>5,6</sup> for existing drug names which sound alike or look alike to Extraneal to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>7</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name Extraneal.

**A. EXPERT PANEL DISCUSSION**

1. OPDRA held an expert panel discussion to gather professional opinions on the safety of the proposed name. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The panel consists of members of OPDRA's medication error safety evaluation staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The Panel believed that Dianeal and Estradiol posed potential risk for look-alike/sound-alike name confusion with the proposed drug name. A product summary is provided in table I on page 4.

2. DDMAC

DDMAC has no objection to the proposed name Extraneal.

---

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> American Drug Index, 42<sup>nd</sup> Edition, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>4</sup> Monthly Prescribing Reference, 17:1 Jan 2001(Murphy JL, Burke J, Speert ML et al., eds) Prescribing Reference Inc., New York

<sup>5</sup> The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

<sup>6</sup> Thomson & Thomson's SAEGIS™ online service: <http://www.thomson-thomson.com>

<sup>7</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

Table I

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Extraneal	7.5% icodextrin, peritoneal dialysis solution	As directed (Single exchange with dwell time of 8-16 hrs)	
Dianeal	1.5% dextrose peritoneal dialysis solution 2.5% dextrose peritoneal dialysis solution 3.5% dextrose peritoneal dialysis solution 4.25% dextrose peritoneal dialysis solution	As directed	LA*
Estradiol	Estradiol oral tablets	1-30 mg/day based on indication and response	LA*
	Estradiol vaginal tablets	25 mcg tab qd x2 wks then 1 q 2 wks	
	Estradiol vaginal cream	1-4 g for 4 weeks then 1 g 1-3x/wk(3 wks on, 1 wk off)	
	Estradiol vaginal ring	1 ring/90 days (7.5 mcg/24 hrs)	
	Estradiol injection	1-30 mg q 2-4 wks	
	Estradiol dermal patch	0.05 mcg/day x2 per wk then 3 wks on 1 wk off cyclically	

\*SA = Sound-alike

\*LA = Look-alike

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Three studies were conducted by OPDRA involving 117 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Extraneal and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Extraneal (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, the verbal order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Table II

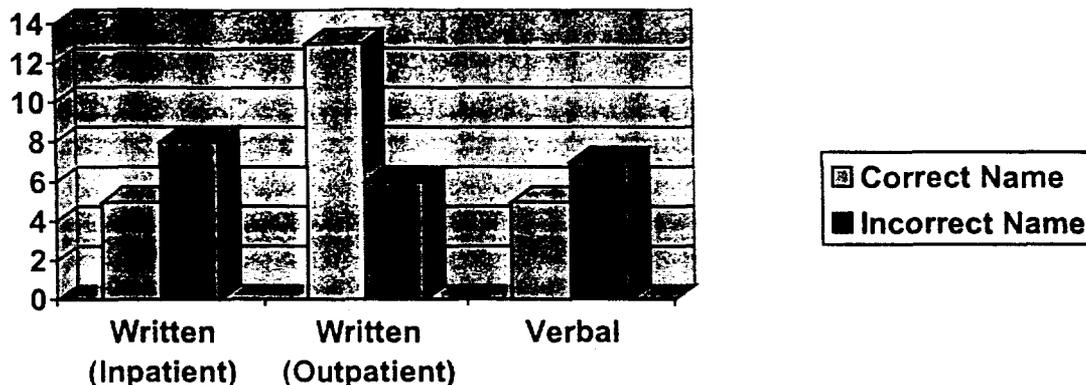
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: Extraneal as directed #10	Verbal Rx: Extraneal as directed #10
Inpatient Rx: Continue Extraneal for 2 more hrs	

### 2. The results are summarized in Table I below.

Table III

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	13 (33%)	5 (38%)	8 (62%)
Written Outpatient	39	19 (49%)	13 (68%)	6 (32%)
Verbal	39	12 (31%)	5 (42%)	7 (58%)
Total	117	44 (38%)	23 (52%)	21 (48%)

## Extraneal



Forty-eight percent of all study participants responded incorrectly to the proposed drug name. Incorrect responses to the written and verbal prescription studies are summarized in Table IV below.

Table IV

Incorrectly Interpreted	
<u>Written Inpatient</u>	Extameal
	Extaneal (4)
	Extianeal
	Extracal
	Extrameal
<u>Written Outpatient</u>	Cytomeal
	Ertraneal
	Ethamol
	Extnaneal
	Extrancal
	Zytramol
<u>Verbal</u>	Extroneal
	Estanyl
	Estranyl
	Extraneil
	Extraneol
	Extranil (2)

All incorrect responses were misspelled or phonetic variations of the proposed drug name. Overall, there were more incorrect responses in the inpatient written study (62%) than in the outpatient written study (32%). This most likely indicates the influence of penmanship on the results. The test results also indicate that respondents had difficulties interpreting both the prefix (Extra) and the suffix (neal). None of the inaccurate responses overlapped with an existing approved drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the name Extraneal, the expert panel believed that Dianeal and Estradiol would be most problematic in terms of potential for name confusion. The names identified look similar to the proposed name.

Dianeal is an isosmotic dialysis solution available in 1.5%, 2.5% 3.5% and 4.25% dextrose. It packaged in 1 and 2 liter bags. The 2 liter Dianeal formulation overlaps with Extraneal which is available in 1.5, 2 and 2.5 liter bags. Although both products are dialysis solutions, there may be a compelling medical reason to use one rather than the other. For example, there is risk of adverse outcome when a patient allergic to cornstarch products is inadvertently exposed to icodextrin. The risk for mix-ups is potentially greater in institutional settings where Dianeal and Extraneal may be stored in close proximity. Since these products have significant home use, there is also a potential risk of sending the wrong product from a distribution point to patients, when names look or sound alike. Although Dianeal and Extraneal share the common suffix "neal", the prefix "Dia" and "Extra" can easily be distinguished. Furthermore, Dianeal comes in 4 strengths therefore a prescription order would require an expression of strength for appropriate dispensing. Moreover, there are no overlapping strengths between the dialysis solutions. In addition, the applicant has developed the following color-coded pull-cap container system to differentiate the products.

Yellow	Dianeal 1.5% dextrose
Green	Dianeal 2.5% dextrose
Natural (White)	Dianeal 3.5% dextrose
Red	Dianeal 4.25% dextrose
Purple	Extraneal

Therefore, the potential risk of product mix-ups between Dianeal and Extraneal appears to be minimal.

Estradiol is an estrogen derivative used in the treatment of menopausal symptoms, female hypogonadism, ovariectomy, primary ovarian failure, palliation of breast cancer and advance prostate carcinoma, metastatic disease and osteoporosis. It is available in variety dosage forms and brand names. Prescription orders for estradiol would indicate the strength, dosage form and route of administration, which are different from Extraneal dialysis solution. Furthermore, Extraneal has a different indication and would not ordinarily be stored in close proximity to estradiol products. Therefore, Estradiol and Extraneal pose minimal risk for name confusion and product mix-ups.

Although none of the inaccurate responses overlapped with an existing approved drug product two responses were close. One of the incorrect responses was Cytomeal, which is close to Cytomel (liothyronine sodium (T<sub>3</sub>)). Another close response was Estanyl, which is close to Estinyl (estinyl estradiol). The potential for mix-up between the proposed name and these products is low in that estinyl and cytomeal are oral tablet dosage as compared to Extraneal peritoneal dialysis solution. The expression of strengths on the oral products is in milligrams and microgram whereas the strength of Extraneal is expressed as a percentage and the volume in liters or milliliters.

### III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the container labels and insert labeling of Extraneal, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error from our review of the current container labels and insert labeling.

1. CONTAINER LABEL (Ultra-Bag and Ambu-Flex containers: .  
  - a. The Rx Only statement should be more prominent.
  - b. The statement "For intraperitoneal administration only" is not noticeable. Please make more prominent.
  - c. Delete the terminal zeros. Express quantitative amount of ingredients as follows:

#### 2 PACKAGE INSERT LABELING

- a. Delete terminal zeros under fill volume in the How Supplied section.

APPEARS THIS WAY  
ON ORIGINAL

**IV. RECOMMENDATIONS:**

OPDRA has no objection to the use of the proposed proprietary drug name Extraneal. However, we recommend implementation of the above labeling revisions to minimize potential user error.

We would appreciate feedback of the final outcome of this consult. We would also be available to meet with the Division for further discussion, if needed. If you have further questions or need more information, please contact David Diwa at 301-827-0892.

*/s/*

---

David Diwa, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

*/s/*

---

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

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this page is the manifestation of the electronic signature.**

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/s/

-----  
David Diwa  
7/16/01 05:07:31 PM  
PHARMACIST

Jerry Phillips  
7/17/01 09:28:49 AM  
DIRECTOR

**Memo to the File**

Date: November 27, 2001

From: Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager, HFD-110

To: NDA 21-321, N(000)

Subject: Pre-Approval Safety Conference Not Needed

In an October 24, 2001 discussion with Dr. Lipicky, he stated that a Pre-Approval Safety Conference (PSC) with the Office of Post-Marketing Drug Risk Assessment (OPDRA) was not necessary for NDA 21-321/Extraneal (icodextrin) Peritoneal Dialysis Solution. I conveyed this to Ms. Susan Lu, OPDRA Team Leader, DDRE I, in an October 24, 2001 telephone conversation. In an email dated October 25, 2001, Ms. Lu wrote: "If Dr. Lipicky feels there are no significant safety issues to relay to OPDRA, it's fine with me not to schedule the PSC" (see attached email).

In a November 5, 2001 response to my October 31, 2001 follow-up email, Ms. Lu agreed that if OPDRA concurred that a PSC was not necessary, then this could be documented with a Memo to the File in DFS (see attached email).

Consequently, a PSC will not be scheduled based on agreement by both the Division of Cardio-Renal Drug Products and OPDRA.

**APPEARS THIS WAY  
ON ORIGINAL**

## Nguyen, Quynh

---

**From:** Lu, Susan  
**Sent:** Monday, November 05, 2001 2:43 PM  
**To:** Nguyen, Quynh  
**Subject:** RE: Extraneal

Sounds great-sorry I haven't gotten back to you earlier as I was on leave most of last week.

Susan

-----Original Message-----

**From:** Nguyen, Quynh  
**Sent:** Wednesday, October 31, 2001 5:10 PM  
**To:** Lu, Susan  
**Subject:** RE: Extraneal

Hi Susan.

Thanks for letting me know. If OPDRA concurs that a PSC for NDA 21-321/Extraneal is not necessary, then I can just do a Memo to the file in DFS. Would that be okay?

Thanks,  
Quynh  
ext. 4-5311

-----Original Message-----

**From:** Lu, Susan  
**Sent:** Thursday, October 25, 2001 5:48 PM  
**To:** Nguyen, Quynh  
**Subject:** Extraneal

Hi Quynh,

If Dr. Lipicky feels there are no significant safety issues to relay to OPDRA, it's fine with me not to schedule the PSC. I will set up a time to talk with Dr. Fredd individually on his medical review. Let me know how you'd like to document this. Thanks much-

Susan

Guzman, John

---

From: Lawrence, John P  
Sent: Monday, July 30, 2001 5:23 PM  
To: 'mary\_kay\_rybicki@baxter.com'  
Cc: Hung, Hsien Ming J; Throckmorton, Douglas C; Guzman, John  
Subject: RE: EXTRANEAL NDA 21-321, Statistical Review



survtime.xpt

Ms. Rybicki,

Dr. Jim Hung and I will be talking to Baxter's statistician at 11:00 am tomorrow. To help identify the problem, I am forwarding a SAS transport file that was sent to me by the company in response to my request in March. I was told that variable 63 (DAYSTILD) is the number of days of follow-up (days till death or loss to follow-up).

Sincerely,  
Dr. John Lawrence

-----Original Message-----

From: mary\_kay\_rybicki@baxter.com [mailto:mary\_kay\_rybicki@baxter.com]  
Sent: Monday, July 30, 2001 2:09 PM  
To: LAWRENCEJ@CDER.FDA.GOV  
Cc: guzmanj@CDER.FDA.GOV  
Subject: EXTRANEAL NDA 21-321, Statistical Review

Dear Dr. Lawrence:

Please see the e-mail to Dr. Throckmorton, below. As discussed earlier today, Frank Ogrinc from Baxter's statistics department and I will be contacting you at 11 am Eastern time to discuss this further. If you have any questions, please do not hesitate to contact me at 847-473-6361.

Sincerely yours,

Mary Kay Rybicki  
Associate Director, Regulatory Affairs  
Baxter Healthcare Corporation

----- Forwarded by Mary Kay Rybicki/Renal/NA/Baxter on 07/30/2001 01:13 PM

-----

Mary Kay

Rybicki

THROCKMORTON@CDER.FDA.GOV

To:

cc:

07/30/2001

Subject: EXTRANEAL NDA

21-321, Statistical Review  
11:41 AM

----- Forwarded by Mary Kay Rybicki/Renal/NA/Baxter on 07/30/2001 11:49  
AM  
-----

Mary Kay

Rybicki

To:

cc: guzmanj@cder.fda.gov

Subject: EXTRANEAL NDA

07/30/2001  
21-321, Statistical Review  
11:18 AM

Dear Dr. Throckmorton:

In response to our telephone conversation of Friday July 26, 2001, Baxter would like to identify the following concerns in the Statistical Review for NDA 21-321, Extraneal (7.5% icodextrin) PDS.

On Page 1 of 7 of the review, section 4 "Results", Dr. Lawrence states that the mortality status of 161 patients was unknown at 375 days of the study, and 168 was unknown at 395 days of the study start. Baxter respectfully disagrees with this interpretation and presentation of study 131.

The original protocol called for 12 months of treatment. Clinical sites were instructed and monitored to ensure patients were followed for 30 days following study completion (12 months) or early termination. The amended protocol (Amendment B) called for 13 month follow-up of all patients identified as early termination who had not terminated due to death or were known to have died following termination. Patient Disposition is described below:

Original Protocol Total Patients Enrolled  
37

Completed 12 Mos. treatment + 30 day follow-up

168

Completed 12 Mos. treatment, identified as death in 30 day

follow-up

1

Withdrew before 12 mos treatment

18

Withdrew due to death 11  
Withdrew, death in 30 day follow-up

6

13 month status unknown 101

Protocol Amendment

13 month status unknown 101

Lost to F/U - IRB Closed 3

Available for Follow-up 98

Totals

Deaths in 13 months

29

(20 icodextrin, 9 control)

Total Known Deaths 34 (22

icodextrin, 12 control)\*

Lost to Follow-up at 13 months 5

IRB Closed 3

Transplanted before 13 months, 2

Of 287 patients enrolled, mortality status of 281 patients was known 13 months following study completion. Six patients were lost to follow-up, 3 due to IRB Closure, two were transplanted prior to 13 months and lost to follow-up, and one remained on PD at last contact, but was lost to follow-up at 13 months.

The numbers described above are in conflict with Dr. Lawrence's statements, on pages 1 of 7 and 5 of 7, in which he concludes that 161 patients were lost to follow-up at 375 days post initiation. It would seem possible that the misinterpretation is the result of the 131 database not including a datapoint for patients that completed 12 months of treatment + 30 days of follow-up unless they had an experienced an AE, SAE or death in that timeframe.

Survival times were calculated based on the documented date in the database, for completors, this date was the last dose date (i.e. -365 days from enrollment). The 30 days of follow-up was not included in the survival time, unless the patient died within this period.

For patients followed-up by the protocol amendment, patient status was obtained 395 days post initiation, and the full 395 days was contributed to the survival analysis.

\*In some cases during the protocol amendment driven follow-up, clinical sites reported patient status beyond the 13 months. This data was included in the database and the mortality analysis of all deaths performed in consultation with Dr. Stephen Fredd, and submitted as an amendment to the FDA.

Baxter is requesting an opportunity to discuss the statistical review with you and Dr. Lawrence at your earliest convenience. Please do not

hesitate  
to contact me at 847-473-6361 if you have any questions or comments.

Sincerely yours,

Mary Kay Rybicki  
Associate Director, Regulatory Affairs  
Baxter Healthcare Corporation

Guzman, John

---

From: mary\_kay\_rybicki@baxter.com  
Sent: Monday, July 30, 2001 2:09 PM  
To: LAWRENCEJ@CDER.FDA.GOV  
Cc: guzmanj@CDER.FDA.GOV  
Subject: EXTRANEAL NDA 21-321, Statistical Review

Dear Dr. Lawrence:

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Sincerely yours,

Mary Kay Rybicki  
Associate Director, Regulatory Affairs  
Baxter Healthcare Corporation

----- Forwarded by Mary Kay Rybicki/Renal/NA/Baxter on 07/30/2001 01:13 PM

Mary Kay  
Rybicki  
THROCKMORTON@CDER.FDA.GOV  
07/30/2001  
21-321, Statistical Review  
11:41 AM  
To:  
cc:  
Subject: EXTRANEAL NDA

----- Forwarded by Mary Kay Rybicki/Renal/NA/Baxter on 07/30/2001 11:49 AM

Mary Kay  
Rybicki  
07/30/2001  
21-321, Statistical Review  
11:18 AM  
To:  
cc: guzmanj@cder.fda.gov  
Subject: EXTRANEAL NDA

Dear Dr. Throckmorton:

In response to our telephone conversation of Friday July 26, 2001, Baxter would like to identify the following concerns in the Statistical Review for NDA 21-321, Extraneal (7.5% icodextrin) PDS.

On Page 1 of 7 of the review, section 4 "Results", Dr. Lawrence states that the mortality status of 161 patients was unknown at 375 days of the study, and 168 was unknown at 395 days of the study start. Baxter respectfully disagrees with this interpretation and presentation of study 131.

The original protocol called for 12 months of treatment. Clinical sites were instructed and monitored to ensure patients were followed for 30 days following study completion (12 months) or early termination. The amended protocol (Amendment B) called for 13 month follow-up of all patients identified as early termination who had not terminated due to death or were known to have died following termination. Patient Disposition is described below:

Original Protocol Total Patients Enrolled		
287	Completed 12 Mos. treatment + 30 day follow-up	
58	Completed 12 Mos. treatment, identified as death in 30 day follow-up	
1		
	Withdrew before 12 mos treatment	
118	Withdrew due to death	11
	Withdrew, death in 30 day follow-up	
6	13 month status unknown	101
Protocol Amendment		
	13 month status unknown	101
	Lost to F/U - IRB Closed	3
	Available for Follow-up	98
Totals		
	Deaths in 13 months	
29	(20 icodextrin, 9 control)	
	Total Known Deaths	34 (22
icodextrin, 12 control)*		
	Lost to Follow-up at 13 months	5
	IRB Closed	3
	Transplanted before 13 months,	2

Of 287 patients enrolled, mortality status of 281 patients was known 13 months following study completion. Six patients were lost to follow-up, due to IRB Closure, two were transplanted prior to 13 months and lost to follow-up, and one remained on PD at last contact, but was lost to

follow-up at 13 months.

The numbers described above are in conflict with Dr. Lawrence's statements, on pages 1 of 7 and 5 of 7, in which he concludes that 161 patients were lost to follow-up at 375 days post initiation. It would seem possible that the misinterpretation is the result of the 131 database not including a datapoint for patients that completed 12 months of treatment + 30 days of follow-up unless they had an experienced an AE, SAE or death in that timeframe.

Survival times were calculated based on the documented date in the database, for completors, this date was the last dose date (i.e. -365 days from enrollment). The 30 days of follow-up was not included in the survival time, unless the patient died within this period.

For patients followed-up by the protocol amendment, patient status was obtained 395 days post initiation, and the full 395 days was contributed to the survival analysis.

In some cases during the protocol amendment driven follow-up, clinical sites reported patient status beyond the 13 months. This data was included in the database and the mortality analysis of all deaths performed in consultation with Dr. Stephen Fredd, and submitted as an amendment to the NDA.

Baxter is requesting an opportunity to discuss the statistical review with you and Dr. Lawrence at your earliest convenience. Please do not hesitate to contact me at 847-473-6361 if you have any questions or comments.

Sincerely yours,

Mary Kay Rybicki  
Associate Director, Regulatory Affairs  
Baxter Healthcare Corporation

Guzman, John

---

From: mary\_kay\_rybicki@baxter.com  
Sent: Monday, July 30, 2001 12:19 PM  
To: throckmorton@cder@fda.gov  
Cc: guzmanj@cder.fda.gov  
Subject: EXTRANEAL NDA 21-321, Statistical Review

Dear Dr. Throckmorton:

In response to our telephone conversation of Friday July 26, 2001, Baxter would like to identify the following concerns in the Statistical Review for NDA 21-321, Extraneal (7.5% icodextrin) PDS.

On Page 1 of 7 of the review, section 4 "Results", Dr. Lawrence states that the mortality status of 161 patients was unknown at 375 days of the study, and 168 was unknown at 395 days of the study start. Baxter respectfully disagrees with this interpretation and presentation of study 131.

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Original Protocol Total Patients Enrolled	
287	
Completed 12 Mos. treatment + 30 day follow-up	
168	
Completed 12 Mos. treatment, identified as death in 30 day follow-up	
1	
Withdrew before 12 mos treatment	
118	
Withdrew due to death	11
Withdrew, death in 30 day follow-up	
6	
13 month status unknown	101
Protocol Amendment	
13 month status unknown	101
Lost to F/U - IRB Closed	3
Available for Follow-up	98
Totals	
Deaths in 13 months	
29	
(20 icodextrin, 9 control)	
Total Known Deaths	34 (22
(12 icodextrin, 12 control)*	
Lost to Follow-up at 13 months	5

Of 287 patients enrolled, mortality status of 281 patients was known 13 months following study completion. Six patients were lost to follow-up, due to IRB Closure, two were transplanted prior to 13 months and lost to follow-up, and one remained on PD at last contact, but was lost to follow-up at 13 months.

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Survival times were calculated based on the documented date in the database, for completors, this date was the last dose date (i.e. -365 days from enrollment). The 30 days of follow-up was not included in the survival time, unless the patient died within this period.

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Sincerely yours,

Mary Kay Rybicki  
Associate Director, Regulatory Affairs  
Baxter Healthcare Corporation

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Revised Draft Labeling

**Date:** October 9, 2001

**Pages including this sheet:** 24

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please find attached the revised draft labeling for NDA 21-321/Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution, which incorporates the Division's comments only. If you have any questions, please feel free to contact me at the above numbers.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

# MESSAGE CONFIRMATION

10/09/01 17:08  
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
733	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
12/09 16:53	06'02"	8474736952	024/024	OK		0000

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

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Revised Labeling for NDA 21-321/Extraneal

**Date:** December 7, 2001

**Pages including this sheet:** 2

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please find attached page 3 of the draft labeling that was faxed to you on December 5, 2001 for NDA 21-321/Extraneal, which has been corrected to remove the words ' \_\_\_\_\_ ' from the subsection header per your telephone message from this morning. This change is acceptable with the medical team leader. If you have any questions, please feel free to contact me at the above numbers.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

# MESSAGE CONFIRMATION

12/07/01 13:02

ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
983	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
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1 pages redacted from this section of  
the approval package consisted of draft labeling

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Revised Labeling for NDA 21-321/Extraneal

**Date:** December 5, 2001

**Pages including this sheet:** 17

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please find attached the draft labeling dated November 14, 2001 for NDA 21-321/Extraneal. The labeling has been revised to reflect the changes agreed upon in response to the December 3, 2001 fax of the revised labeling. The additional minor editorial corrections that I pointed out to you in our telephone conversation this morning have also been included. Please let me know if you have any questions, or if there are any changes that Baxter does not agree with.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

# MESSAGE CONFIRMATION

12/05/01 12:18  
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
216	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
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**Transmitted to FAX Number:** (847) 473-6952  
**Attention:** Ms. Mary Kay Rybicki  
**Company Name:** Baxter Healthcare Corporation  
**Phone:** (847) 473-6361  
**Subject:** Revised Labeling for NDA 21-321/Extraneal  
**Date:** December 5, 2001  
**Pages including this sheet:** 17

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

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Revised Labeling for NDA 21-321/Extraneal-Correction to Page 6

**Date:** December 3, 2001

**Pages including this sheet:** 2

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please note that there should be a correction to the revised labeling dated November 14, 2001 that I just faxed to you. On page 6, under **PRECAUTIONS/Information for Patients**, the statement following

\_\_\_\_\_ " should be "(See  
**PRECAUTIONS, Drug/Laboratory Test Interactions.)**" instead of \_\_\_\_\_  
This corrected page is attached. If you have any questions, please  
feel free to contact me at the above numbers.

Thanks,  
Quynh

# MESSAGE CONFIRMATION

12/03/01 19:26  
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
198	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
12/03 19:25	00'49"	8474736952	002/002	OK		0000

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**Transmitted to FAX Number:** (847) 473-6952  
**Attention:** Ms. Mary Kay Rybicki  
**Company Name:** Baxter Healthcare Corporation  
**Phone:** (847) 473-6361  
**Subject:** Revised Labeling for NDA 21-321/Extraneal-Correction to Page 6  
**Date:** December 3, 2001  
**Pages including this sheet:** 2

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

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Revised Labeling for NDA 21-321/Extraneal

**Date:** December 3, 2001

**Pages including this sheet:** 17

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please find attached the draft labeling dated November 14, 2001 for NDA 21-321/Extraneal. The labeling has been revised to reflect the changes based on discussions with the Division following the November 9, 2001 teleconference. Additionally, minor editorial corrections were made. Please let me know if you have any questions, or if there are any changes that Baxter does not agree with.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

# MESSAGE CONFIRMATION

12/03/01 19:00  
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
197	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
12/03 18:55	05'23"	8474736952	017/017	OK		0000

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**Attention:** Ms. Mary Kay Ryhicki  
**Company Name:** Baxter Healthcare Corporation  
**Phone:** (847) 473-6361  
**Subject:** Revised Labeling for NDA 21-321/Extraneal  
**Date:** December 3, 2001  
**Pages including this sheet:** 17

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Mary Kay Rybicki

**Company Name:** Baxter

**Phone:** (630) 355-2257

**Subject:** marked up labeling/Extraneal

**Date:** 11/7/01

**Pages including this sheet:** 16

**From:** Colleen LoCicero

**Phone:** 301-594-5332

**Fax:** 301-594-5494

Mary Kay,

Here it is. Let me know if there is anything you can't read.

Regards,  
Colleen

# MESSAGE CONFIRMATION

11/07/01 16:15  
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
974	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
11/07 16:10	04'54"	8474736952	016/016	OK		0000

## DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



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**Transmitted to FAX Number:** (847) 473-6952  
**Attention:** Mary Kay Rybicki  
**Company Name:** Baxter  
**Phone:** (630) 355-2257  
**Subject:** marked up labeling/Extraneal  
**Date:** 11/7/01  
**Pages including this sheet:** 16  
**From:** Colleen LoCicero  
**Phone:** 301-504-5327

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

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

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**Transmitted to FAX Number:** (847) 473-6952

**Attention:** Ms. Mary Kay Rybicki

**Company Name:** Baxter Healthcare Corporation

**Phone:** (847) 473-6361

**Subject:** Action Letter

**Date:** October 22, 2001

**Pages including this sheet:** 32

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Mary Kay,

Please find attached the action letter and revised draft labeling for NDA 21-321/Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution. If you have any questions, please feel free to contact me at the above numbers.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

# MESSAGE CONFIRMATION

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**Transmitted to FAX Number:** (847) 473-6952  
**Attention:** Ms. Mary Kay Rybicki  
**Company Name:** Baxter Healthcare Corporation  
**Phone:** (847) 473-6361  
**Subject:** Action Letter  
**Date:** October 22, 2001  
**Pages including this sheet:** 32  
**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 504 5211