CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Administrative Documents

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-321		
Drug: Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution	Applicant: Baxter Healthcare Corporation	
RPM: Russell Fortney	HFD-110	Phone # 594-5311
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM-10/10/01 & 11/5/02
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-October 22, 2001
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Final Printed Labeling	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC-2/18/01, 2/14/02, 5/7/02, ODS-7/16/01, 11/16/01, 2/27/02, 9/12/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (see Approval Letter)
• Documentation of discussions and/or agreements relating to post-marketing commitments	X (11/5/02 Telecon minutes)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 12, 1997 & August 6, 1997
• Pre-NDA meeting (indicate date)	October 4, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	September 27, 2002
• Other	October 4, 2002

❖ Advisory Committee Meeting	
• Date of Meeting	August 9, 10, 2001
• 48-hour alert	Quick Minutes
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	OD-October 29, 2001 DD-October 12, 2001
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	June 8, 2001
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	July 12, 2001
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	December 28, 2001
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	May 7, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	December 22, 2000, August 31, 2001
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	September 10, 26, 2001, December 12, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	September 10, 2000
• Review & FONSI *(indicate date of review)*	X
• Review & Environmental Impact Statement *(indicate date of each review)*	X
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	July 9, 2001
❖ Facilities inspection (provide EER report)	Date completed: September 10, 2002 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	To be initiated
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 15, 2001
❖ Nonclinical inspection review summary	Memorandum Date: May 28, 1998
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	Memorandum Date: May 28, 1998
❖ CAC/ECAC report	Memorandum Date: May 28, 1998

Time Sensitive Patent Information
Pursuant to 21 CFR 314.53
For NDA # 21-321

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Extraneal
Active Ingredient:	icodextrin
Strength:	7.5% w/v
Dosage Form:	Peritoneal Dialysis Solution
Approval Date:	Pending

U.S. Patent Number: 4,761,237

Expiration Date: August 2, 2005

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) No
2. Drug Product (Composition Formulation) No
3. Method of Use Yes

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:
Peritoneal Dialysis Solution

Name of Patent Owner: Baxter International Inc., the parent corporation of Baxter Healthcare Corporation, the sponsor of this application.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

The undersigned declares that the above stated United States Patent Number 4,761,237 covers the composition, formulation and/or method of use of Extraneal (name of drug product). This product is the subject of this application for which approval is being sought.

Signed: Mary Kay Rybicki Mary Kay Rybicki

Date: November 6, 2001

Title: Associate Director, Regulatory Affairs

Telephone Number: 847-473-6361

U.S. Patent Number: 4,886,789

Expiration Date: December 12, 2006

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) **No**
2. Drug Product (Composition Formulation) **No**
3. Method of Use **Yes**

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:
Peritoneal Dialysis Solution.

Name of Patent Owner: ML Laboratories PLC, London, England

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

Mr. Bruce Manning,
New England Biomedical Research Inc.,
96 West Main Street,
Northborough, MA 01532

The undersigned declares that the above stated United States Patent Number 4,886,789 covers the composition, formulation and/or method of use of Extraneal (name of drug product). This product is the subject of this application for which approval is being sought.

This patent is licensed to Baxter Healthcare S.A. and all associated companies of Baxter Healthcare S.A. including Baxter Healthcare Corporation, who are affiliates of Baxter International, Inc. The License between ML Laboratories, PLC and Baxter Healthcare S.A. has been recorded with the United States Patent and Trademark Office on November 22, 1999, Reel 010235, Frame 0013.

Signed: Mary Kay Rybicki Mary Kay Rybicki

Date: November 6, 2001

Title: Associate Director, Regulatory Affairs

Telephone Number: 847-473-6361

U.S. Patent Number: 6,077,836

Expiration Date: June 20, 2017

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) **No**
2. Drug Product (Composition Formulation) **Yes**
3. Method of Use **No**

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: ML Laboratories PLC, London, England

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

Mr. Bruce Manning,
New England Biomedical Research Inc.,
96 West Main Street,
Northborough, MA 01532

The undersigned declares that the above stated United States Patent Number 6,077,836 covers the composition, formulation and/or method of use of Extraneal (name of drug product). This product is the subject of this application for which approval is being sought.

This patent is licensed to Baxter Healthcare S.A. and all associated companies of Baxter Healthcare S.A. including Baxter Healthcare Corporation, who are affiliates of Baxter International, Inc. The License between ML Laboratories, PLC and Baxter Healthcare S.A. has been recorded with the United States Patent and Trademark Office on November 22, 1999, Reel 010235, Frame 0013.

Signed: Mary Kay Rybicki Mary Kay Rybicki

Date: November 6, 2001

Title: Associate Director, Regulatory Affairs

Telephone Number: 847-473-6361

U.S. Patent Number: 6,248,726 B1

Expiration Date: June 19, 2018

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) No
2. Drug Product (Composition Formulation) No
3. Method of Use Yes

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Peritoneal Dialysis Solution.

Name of Patent Owner: ML Laboratories PLC, London, England

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

Mr. Bruce Manning,
New England Biomedical Research Inc.,
96 West Main Street,
Northborough, MA 01532

The undersigned declares that the above stated United States Patent Number 6,248,726 B1 covers the composition, formulation and/or method of use of Extraneal (name of drug product). This product is the subject of this application for which approval is being sought.

This patent is licensed to Baxter Healthcare S.A. and all associated companies of Baxter Healthcare S.A. including Baxter Healthcare Corporation, who are affiliates of Baxter International, Inc. The License between ML Laboratories, PLC and Baxter Healthcare S.A. has been recorded with the United States Patent and Trademark Office on November 22, 1999, Reel 010235, Frame 0013.

Signed: Mary Kay Rybicki Mary Kay Rybicki

Date: November 6, 2001

Title: Associate Director, Regulatory Affairs

Telephone Number: 847-473-6361

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

PATENT INFORMATION

Pursuant to 21 CFR 314.53 (c), Baxter Healthcare Corporation submits the following patent information for Extraneal™ (7.5% icodextrin) Peritoneal Dialysis Solution.

U.S. Patent No.	Expiration Date	Type of Patent
4,761,237	August 2, 2005	Drug Product, Method of Use in Peritoneal Dialysis
4,886,789	December 12, 2006	Drug Product

The undersigned declares that U.S. Patent Nos. 4,761,237 and 4,886,789 cover the formulation, composition, and/or method of use of Extraneal™ (7.5% icodextrin) Peritoneal Dialysis Solution. This product is the subject of this application for which approval is being sought. The owner of U.S. Patent No. 4,886,789 is ML Laboratories PLC, London, England. The U.S. Agent for ML Laboratories is Mr. Bruce Manning, New England Biomedical Research Inc., 96 West Main Street, Northborough, MA 01532. This patent is licensed to Baxter Healthcare S.A. and all associated companies of Baxter Healthcare S.A. including Baxter Healthcare Corporation, who are affiliates of Baxter International, Inc. The License between ML Laboratories, PLC and Baxter Healthcare S.A. has been recorded with the United States Patent and Trademark Office on November 22, 1999, Reel 010235, Frame 0013. The owner of U.S. Patent No. 4,761,237 is Baxter Healthcare Corporation, the sponsor of this application.

Baxter Healthcare Corporation believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to a claim of patent infringement could be reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Steven Engel, MS. PharmD.
Vice President, Global Regulatory Affairs
Baxter Healthcare Corporation

12/14/00
Date

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

CLAIM FOR EXCLUSIVITY

Pursuant to 21 CFR 314.31, Baxter Healthcare Corporation claims a period of marketing exclusivity for Extraneal™ (7.5% icodextrin) Peritoneal Dialysis Solution. Extraneal is entitled to seven years exclusivity per 21 CFR 316.31. To the best of Baxter Healthcare Corporation's knowledge, no drug containing 7.5% icodextrin has previously been approved under section 505 (b) of the Food Drug and Cosmetic Act. As a result, no 505(b) or abbreviated new drug application may be approved for drug products containing 7.5% icodextrin until seven years of the date of marketing approval for Extraneal™.

Steven A. Engel

November 30, 2000

Steven Engel, MS. PharmD.
Vice President, Global Regulatory Affairs
Baxter Healthcare Corporation

Date

EXCLUSIVITY SUMMARY FOR NDA # 21-321 Supplement # Original NDA

Trade Name: Extraneal (7.5% icodextrin) Generic Name _____
Applicant: Baxter Healthcare HFD# 110
Approval Date If Known: _____

PART I - IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /☒/ NO /☐/

   b) Is it an effectiveness supplement?

   YES /☐/ NO /☒/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /☒/ NO /☐/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity. EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /☒/ NO /☐/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **7 years**

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /☐/ NO /☒/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /☐/ NO /☒/

If yes, NDA#: _____ Drug Name: _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Is this drug product or indication a DESI upgrade?

YES /☐/ NO /☒/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /☐/ NO /☒/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	Active Moiety

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /☐/ NO /☒/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	Active Moiety

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /☐/ NO /☐/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /☐/ NO /☐/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /☐/ NO /☐/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /☐/ NO /☐/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /☐/ NO /☐/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /☐/	NO /☐/
Investigation #2	YES /☐/	NO /☐/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /☐/	NO /☐/
Investigation #2	YES /☐/	NO /☐/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not

"new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

   a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

   Investigation #1

   IND # _____ YES /☐/ NO /☐/ Explain: _____

   Investigation #2

   IND # _____ YES /☐/ NO /☐/ Explain: _____

   (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

   Investigation #1

   YES /☐/ Explain _____ NO /☐/ Explain _____

   Investigation #2

   YES /☐/ Explain _____ NO /☐/ Explain _____

   _____ _____

   _____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /☐/ NO /☐/

If yes, explain: _____

_____ _____

Signature Date

Title: Consumer Safety Officer

_____ _____

Signature of Office Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

/s/

Raymond Lipicky
9/26/01 02:58:02 PM

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021321	**Trade Name:**	EXTRANEAL(ICODEXTRIN)7.5%W/V PD SOLUTION
Supplement Number:	000	**Generic Name:**	ICODEXTRIN
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF CHRONIC RENAL FAILURE
Action Date:	12/22/00		

Indication # 1	Extraneal is indicated for a single daily exchange for the long (8 - 16 hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of chronic renal failure.
Label Adequacy:	Other - See Comments
Formulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	Baxter Healthcare requested a waiver from pediatric use information, in accordance with 21 CFR 314.55 (d). The requirement for pediatric use information has been waived because the drug has been granted orphan status.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	Adult	Waived	

Comments: Orphan Waiver-see above.

This page was last edited on 10/3/01

Signature /S/ _____ 10/3/01 Date

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

EXEMPTION FROM PEDIATRIC USE INFORMATION

Pursuant to 21 CFR 314.55(d), Baxter HealthCare Corporation is claiming an exemption of the requirements of 21 CFR 314.55 (a) for pediatric use information.

The product for which Baxter is seeking marketing approval, Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution, received Orphan Drug Designation 97-1056 on July 18, 1997. Clinical studies conducted in support of NDA 21-321 did not include patients under the age of 18. The intended population for the product that is the subject of NDA 21-321 is patients aged 18 and older.

NDA 21-321
EXTRANEAL (7.5% icodextrin)
Peritoneal Dialysis Solution

DEBARRMENT CERTIFICATION

Baxter Healthcare Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Steven Engel, MS, Pharm.D.
Vice President, Global Regulatory Affairs
Baxter Healthcare Corporation

November 30 2000
Date

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 2001

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Approvable action on Extraneal (7.5% icodextran peritoneal dialysis solution) – NDA 21-321

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

Your memorandum addresses most issues that arose during review and I agree with your conclusions, notably that (1) Extraneal is approvable for use as a peritoneal dialysis solution; (2) that (based on the labeling you forwarded) its use need not be restricted to patients inadequately responding to dextrose (Dr. Fredd had suggested such a limitation); and (3) that there not be a long-term post-marketing active control mortality study (also suggested by Dr. Fredd). I would like to comment briefly on points (2) and (3).

There are five randomized trials (4 efficacy trials plus DIANA) in NDA 21-321. Although only Study 131 was identified as a mortality study, studies 130, MIDAS, and Pro-Renal-Reg 035. also (obviously) had survival data for 1-6 months duration and DIANA had 2 year data. All trials were active control comparisons to 2.5% dextrose except for MIDAS, which also had 1.5% and 4.5% groups. Icodextrin was consistently superior to 1.5 and 2.5% on ultrafiltration (volume drained – volume infused) and on creatinine and BUN clearance. Mortality was:

	Deaths				
	Sample		Deaths		
Study	ICO	Control	ICO	Control	p value
130 (4 week)	90	85	0	0	---
131 (52 wk) (ITT)	175	112	13 22	5 12	(log-rank) 0.336
MIDAS (6 mos)	103	106	1	2	
Pro-Renal (16 week)	20	19	1 (3) (2 p study)	0	
DIANA (2 yr)	19	19	0	6	
Total	407	341	26 (0.63)	20 (0.59)	

The table shows full ITT result for Study 131 (22 vs. 12) and counts all 3 Extraneal deaths in Pro-Renal, although 2 were shortly post-study.

My numbers are somewhat different from yours and Dr. Fredd's, which do not include study 130 (4 week), but the other 4 studies give:

	Extraneal	Glucose
N	320	253
Deaths	26	20
% death	8.1%	7.9%

I'm not sure why the numbers differ, but whether considering crude rates or a p value based on log-rank test of mortality over time (p=0.929), there is nothing here.

The "no finding" conclusion is, of course, partly driven by the 0 vs. 6 (Extraneal vs. glucose) finding in DIANA but that illustrates the hazards of small numbers. The DIANA finding is no more nor less plausible than the study 131 finding and the 131 finding does not approach statistical significance. As you note, nothing about the deaths seems unusual for this population. There is thus no reason not to attribute all of these findings to chance. There is also no plausible mechanism that would make us think an adverse survival effect of Extraneal is plausible, much less likely. Given that, and the dead-on mortality and survival data, I do not think the available data are less than reasonable or necessarily less than desirable, considering the therapeutic area and past practice. The CRAC apparently agreed.

Given the absence of any signal of increased risk and the lack of any reason to expect one (the even results of trials, non-suggestive nature of the observed deaths, and lack of plausible mechanisms) I do not think approval needs to be conditioned on conduct of a large, long-term comparative trial, nor do I think Extraneal need be reserved for patients failing glucose-based dialysis.

/S/

Robert Temple, M.D.

cc:
Orig. NDA 21-321
HFD-110
HFD-110 Project Manager
HFD-101/R Temple
drafted:sb/10/23/01
final:sb/10/29/01
Filename:Extraneal_MM_Oct01.doc

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

/s/

Sandra Benton
10/30/01 09:06:14 AM
TECHNICAL

Robert Temple
11/1/01 07:06:18 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division or Cardio-Renal Drug Products — **Memorandum**

Date : 10/12/01
From : Director, Division of Cardio-Renal Drug Products, HFD-110
Subject : Approvablility of NDA 21-321, EXTRANEAL®, Baxter Healthcare Corporation
To : Director, Office of Drug Evaluation I, HFD-100

Introduction

Extraneal® is marketed in about 28 countries worldwide. There has been some [redacted] months of exposure, worldwide. This experience has alerted Baxter Healthcare Corporation to only one apparent signal, namely skin rashes.

Extraneal® is a peritoneal dialysate solution that differs from others in that the osmotic agent is 7.5% Icodextrin, a colloidal osmotic agent that is a starch derived, glucose polymer with a weight average molecular weight between [redacted] Daltons. Icodextrin is absorbed, distributes systemically and therefore Extraneal® is considered a new chemical entity; although peritoneal dialysate solutions are common. The results contained in NDA 21-321 were reviewed by the Cardiac and Renal Drugs Advisory Committee on August 9, 2001 and the Advisory Committee recommended that Extraneal® be approved.

The NDA database includes observations pertinent to 493 patients who received Extraneal® for a mean duration of 232.5 days, median duration of 169 days, and maximum duration of 1326 days. There is no question that it is a peritoneal dialysis solution, and that it has ultrafiltration properties different from 1.5%, 2.5% and 4.25% dextrose containing standard approved peritoneal dialysis solutions. Thus, Extraneal® should be considered to be life saving, since the historical control expectation is that patients who require peritoneal dialysis would have a life expectancy, without dialysis, of only 10s of days.

Baxter Healthcare Corporation has been involved in developing and marketing peritoneal dialysis solutions for a long time. Their most recent FDA history started around 1988. They have been through 5 different FDA Divisions, finally resting in the Division of Cardio-Renal Drug Products in 1997 with [redacted] Since that time there have been numbers of internal meetings (the Division and Office), meetings between the Division and Baxter, and Baxter has been to the Cardiac and Renal Drugs Advisory Committee two times excluding the time when the Advisory Committee met regarding the approvability of Extraneal®. The Extraneal® development program (the contents of NDA 21-321) was not guided solely by Baxter Healthcare Corporation.

I think Extraneal® should be approved, the Divisions marked-up package insert is attached, a draft approvable letter is also attached. However, this recommendation is not without several lingering problems.

Problems

1) Chemistry

The Division's co-located consulting chemists had no material outstanding questions and accepted the stability testing data as satisfactory for an expiry date of only18 months. The field inspection of the manufacturing sites found everything to be satisfactory. Our Office of Compliance disagreed with these evaluations and has asked that the we withhold approval of this NDA until they have resolved a general

problem with Baxter Healthcare Corporation, not just with respect to Extraneal®, but also with respect to several other approved products (although they do not recommend withdrawal of the other products from the market).

At the time of this writing I can not explain the nature of the problem, except to say that Baxter Healthcare Corporation as a Corporate policy reports the results of stability testing in a fashion that the Office of Compliance thinks the results as reported do not allow appraisal of stability.

For our purposes, now, that is easy enough to resolve. The approvable letter contains a paragraph that says, approvable—once you have resolved the issues raised by the Office of Compliance—.

2) Hypertension

Although not any issue during the initial review, at the August 2001 Advisory Committee meeting, Baxter Healthcare showed a slide that caused the Advisory Committee members to be concerned with the possibility that blood pressure rose excessively when patients were dialyzed with Extraneal®. That resulted in the submission of an amendment (8/30/01) that was reviewed by Dr. Fredd (9/21/01). It is clear that the data do not show any increase in blood pressure in Extraneal® treated patients, and that the slide shown at the Advisory Committee was an inadvertent misrepresentation of data that should be seriously considered. So this is not a problem.

3) Safety (Mortality)

Here is where there is something to discuss, although it is not entirely clear to me what needs to be highlighted, nor what knowledge or policy needs to be brought to bear. A pretty clear, at least to me, outcome of our internal discussions and the Advisory Committee meetings (those that dealt with only what should a development program look like; which all preceeded the Extraneal® meeting where approval was recommended) was:

> Provided that there was no "claim" associated with a new peritoneal dialysis solution, that is no claim that it was something other than another "I am also another dialysate", the development program needed to do no more than show it was a dialysate (not very many patients) and that it did no obvious harm. In other words a few hundred patients would suffice as a total program (the Sponsor heard the numbers 400 to 800 total patients).

The Extraneal® development program evolved as a consequence of this understanding. The Advisory Committee recommended approval based on this general philosophy.

Overall, from 4 controlled clinical trials (glucose containing peritoneal dialysate being the control, and the duration of studies varying from16 weeks to 2 years) the observed all-cause mortality is summarized in the following table. The p value for the difference between groups was 0.929 (LogRank test comparing survival cures between groups).

Treatment Group	Number of Patients	Number of Deaths	%
Control	285	20	7.0
Extraneal®	366	26	7.1

Clearly there is no suggestion here of any obvious harm on survival LogRank p-value = 0.929), but equally clearly there were not many events so confidence limits are wide. The mean death rates were 0.11 per 100 patient years in both groups. Differences in mortality rates (per year; Extraneal – control) had 90% confidence bounds of –0.51 to 0.053 around a difference of 0.001. So the question is, is this good enough? I think so. Although its adequacy can be debated, it is more comparative information than anyone has with respect to any approved peritoneal dialysis regimen in existence.

In so saying, I haven't a quantitative leg to stand on, I have no regulatory precedent to cite and I have no "safety" standard to quote. In addition, the one study that was "designed" to purposefully evaluated the "safety", study 131 (all patients are accounted for up to 13 months), where the mortality for the Extraneal® relative to the control group was 1.51 (95% confidence limits 0.686 and 3.30). In spite of all that I think the 7.0 vs. 7.1% is "O.K.".

The number of events is small and confidence limits are wide. This is exemplified if one looks at mortality results by study.

Study Name	Treatment Group	Number of Patients	Number Deaths	%	Duration
131	Control	112	12	10.7	
	Extraneal®	175	22	12.6	1 year
MIDAS	Control	103	2	1.9	
	Extraneal®	106	1	0.9	6 months
PRO-RENAL	Control	19	0	0	
	Extraneal®	20	3	15	16 weeks
DIANA	Control	19	6	31.6	
	Extraneal®	19	0	0	2 years

So I argue that the pooled analysis gives the "best" estimate of the treatment effect. If I could pick and choose among the results, I would pick the longest study (2 years on peritoneal dialysis) and argue that one could surmise a mortality benefit of Extraneal®, or the next "largest" study where once again one might surmise a mortality benefit of Extraneal®. Obviously the number of events is too small (in total or in any study) to conclusively show anything and any subdivision of results I elected to choose would be bad judgment and a poor argument.

The nature of the deaths observed in the Extraneal® groups is worth taking a brief look. They include things such as peritonitis (a few), myocardial infarction (a few), gangrene, pneumonia, sepsis, cardiac arrest, diabetic coma, CVA, congestive heart failure, etc. A wash-list, which suggests nothing to me. Of the patients that died of stroke and were Extraneal® treated (page 9 of Dr. Fredd's review of the 8/30/01 amendment), those particular patients had a decrease (from baseline) in their systolic blood pressure. So there is nothing I can see, from a mechanistic point of view that would put Extraneal® under some high suspicion of something or another.

Without further agonizing, I readily admit that we recommended and Baxter Healthcare executed an overall program that was less than ultimately desirable. But, again, I assert that it is enough for approval. The overall observations are 7.0% mortality in the control and 7.1% in the Extraneal® groups.

4) Safety (Other)

One of more serious adverse events was present in 31.7 and 31.2% of patients, Extraneal® and control groups, respectively. Peritonitis was the single most frequent reported serious adverse event, 5.3 and 8.6% (Extraneal® and control groups, respectively). In perusing the serious adverse events, neither the sponsor, Dr. Fredd nor I were able to find any events that appeared to need further exposition, nor that appeared to have any bearing upon the issues of approval.

Infection during peritoneal dialysis is in general a major problem. Indeed, the overall incidence of peritonitis (including serious) was 26.4 and 25.4 %, and of exit site infection was 14.8 and 16.7 (Extraneal® and control groups, respectively). There is no signal here.

Two items, perhaps related to the systemic absorption of icodextrin, need some exposition.

- Skin rash was reported in 10.1 and 4.6% of patients (Extraneal® and control groups respectively). Nine of the Extraneal® treated patients and one control treated patients were reported to have exfoliative dermatitis. None of these (10) patients were seen by a dermatologist. This particular rash did not involve the entire body, being mainly limited to palms and soles, but were characterized by flaking of the skin. They were simply exfoliative dermatitis by CoStart term, and probably misclassified by the nephrologist investigators. There were no suggestions of immunologic disorder anywhere in the database. The increased incidence of skin reactions is noted in the package insert but the terminology of exfoliative dermatitis is not mentioned.

- Alkaline phosphatase was increased by about 20 U/L (change from baseline; Extraneal® minus control) throughout the entire observation periods (up to two years). Other liver function was unchanged, on average. The meaning of this finding is unclear, and the values were within the range of alkaline phosphatase that is seen in patients with end stage renal disease. This is noted in the package insert.

Icodextrin is a competitive inhibitor of the substrate used by standard clinical assays for serum amylase activity, consequently serum amylase is artefactualy lowered in patients receiving Extraneal® peritoneal dialysis. This is noted in the package insert.

5) Certification: Financial interests and arrangements with clinical investigators.

We are in receipt of Form 3454 and Forms 3455 from the Sponsor. This submission has not been previously reviewed, so it is here. Form 3454 listed 109 investigators as not having financial arrangements characterized by checkbox 1. I see no reason to question this certification.

Forms 3455 list 5 investigators that received payments for doing studies on or after February 2, 1999, and

Each of these investigators were involved in study 130 and 131 (the study that found an adverse (the control was favored) mortality point estimate for Extraneal®. I see nothing unusual in the disclosure, except that its receipt if recorded here.

Summary

The comments of Chemistry, Pharmacology, Clinical Pharmacology and Medical are incorporated in the marked-up package insert attached. An approvable letter is attached for your signature.

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

/s/

Raymond Lipicky
10/12/01 02:51:54 PM
MEDICAL OFFICER

TO: NDA 21321 9/21/01
FROM: Stephen Fredd, M.D.
Subject: Amendment 8/30/01

At the 8/9/01 meeting of the CardioRenal Advisory Committee, members voiced concern about the possible excess of cardiovascular deaths in the Icodextrin treated patients, and the possible relationship of that to the hypothesis that Icodextrin elevated systolic blood pressure. They requested that further analyses of the blood pressure data from study 131 including shift data and results of blood pressure in those who died be provided. On 8/30/01 the sponsor presented the data as box plots and graphic display without numerical information. A request for numerical presentations of these data was made, and these data are included in this review. The amendment also included proposed labeling changes based on input from reviewers.

BLOOD PRESSURE AND MORTALITY

Using the 13 month follow-up mortality result of 9/112 (8%) versus 20/175 (11.4%) in placebo and Icodextrin cohorts respectively, the following list gives information on cause of death divided by APD and CAPD strata.

APD	Control	39	1501	289	328	UNKNOWN
	Icodextrin	10	19503	64	279	CARDIAC
		9	26503	15	23	Sepsis and metabolic acidosis as a consequences of retroperitoneal gangrene and peritonitis following renal transplant
		55	30501	108	123	Heart Attack
		56	45401	15	39	Cardiac Arrest
		44	61603	69	219	CARDIAC ARREST, CAUSE UNKNOWN
		93	62501	49	49	Myocardial Infarction
CAPD	Control	35	15202	53	177	UNKNOWN
		17	18102	160	160	Cardiac Arrest
		20	21205	223	223	Cardiac Arrest
		25	22102	303	303	Acute Necrotizing Bronchopneumonia
		124	32401	274	359	CARDIAC ARREST, CAUSE UNKNOWN
		121	35101	113	113	Myocardial Infarction
		126	40301	367	395	Pneumonia and Heart Failure
		58	43403	138	361	MULTI SYSTEM ORGAN FAILURE
	Icodextrin	11	2401	52	176	CEREBROVASCULAR ACCIDENT INCLUDING INTRACRANIAL HEMORRHAGE
		22	6102	78	78	Electro-mechanical Dissociation
		53	11601	133	138	Heart Arrest
		17	18106	148	148	Cardiac Arrest
		25	22106	226	241	Myocardial Infarction
		25	22202	324	324	Myocardial Infarction
		52	27102	169	169	Acute Cardiac Arrest
		55	30302	164	164	Natural Causes (exact unknown)
		124	32301	108	293	WITHDREW FROM DIALYSIS D/T ESCALATION OF SEVERE PERIPHERAL VASCULAR DISEASE, DIABETES MELLITUS - 20-NOV-1999
		121	35301	91	156	RENAL FAILURE
		121	35401	206	208	Cerebrovascular Accident
		57	38102	206	256	END STAGE RENAL DISEASE
		57	38103	254	364	PERIPHERAL VASCULAR DISEASE PER DEATH CERTIFICATE. END STAGE RENAL DISEASE (L) ABOVE KNEE AMPUTATION.
		47	42302	363	363	Bowel Infarct post Myocardial Infarction

Members of the advisory committee thought there were more cardiovascular deaths (particularly strokes) in the Icodextrin group compared to control. To respond to their follow-up question regarding systolic blood pressure change from baseline, the sponsor provided the following data:

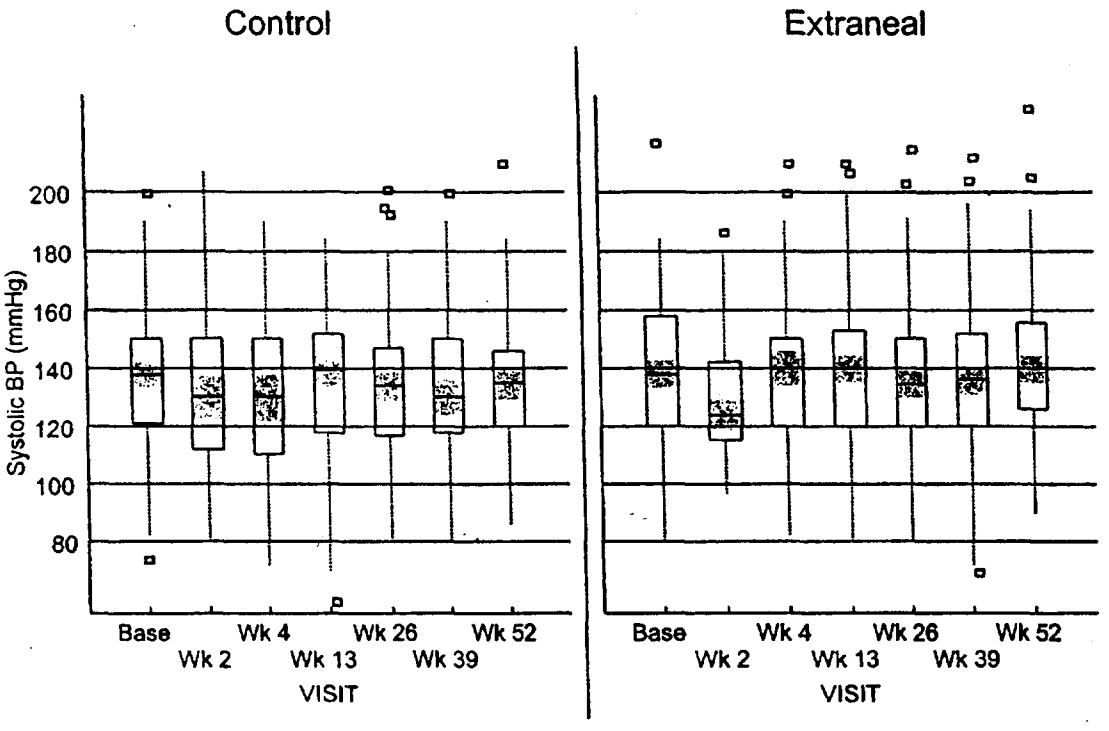
Vital Sign	Visit	Treatment Group	Baseline @ Mean	Data N	Mean	Std Err	Min	Median	Max	Change from Baseline @ Mean	Std Err	p Wthn	Min	Median	Max	p Betw
Systolic BP (mmHg), Sitting	Baseline	Control		113	136.34	2.21		138.00	200.[illegible]							0.711
	(Week 0)	Icodextrin		175	137.31	1.81		138.00								
	Week 2	Control	132.84	63	131.58	3.38		130.00		-1.26	2.64	0.689		-1.00		0.317
		Icodextrin	134.15	67	130.64	2.58		134.00		-3.51	2.36	0.023		-3.00		
	Week 4	Control	132.84	63	130.33	3.09		130.00		-2.61	2.30	0.266		-1.50		0.108
		Icodextrin	134.15	67	137.16	3.29		140.00		1.01	2.83	0.730		0.00		
	Week 13	Control	134.84	94	133.71	2.65		130.50		-3.15	2.64	0.240		0.00		0.345
		Icodextrin	137.19	143	137.14	2.07		140.00		0.00	2.04	0.981		-0.50		
	Week 26	Control	136.84	83	133.58	2.61		134.00		-4.68	2.74	0.106		-4.00		0.334
		Icodextrin	137.19	130	136.15	2.30		134.50		-1.85	2.21	0.436		0.00		
	Week 39	Control	136.96	70	133.36	2.65		136.00		-3.79	2.90	0.206		-4.00		0.331
		Icodextrin	137.79	111	137.81	2.04		136.00		0.03	2.03	0.995		-4.00		
	Week 52	Control	136.47	63	134.18	2.88		138.00		-2.29	3.39	0.498		-4.50		0.073
		Icodextrin	136.53	104	140.70	2.36		140.00		4.19	2.81	0.142		2.00		
Diastolic BP (mmHg), Sitting	Baseline	Control		113	78.38	1.36		79.00								0.330
	(Week 0)	Icodextrin		175	79.79	0.93		80.00								
	Week 2	Control	78.83	63	77.54	1.72		80.00		-0.30	1.56	0.845		0.00		0.454
		Icodextrin	78.69	67	76.93	1.40		78.00		-1.76	1.36	0.200		0.00		
	Week 4	Control	78.83	63	78.83	1.59		80.00		0.00	1.57	1.000		0.00		0.550
		Icodextrin	78.69	67	79.66	1.83		80.00		0.97	1.44	0.505		0.00		
	Week 13	Control	77.97	94	78.21	1.35		80.00		0.24	1.64	0.836		0.00		0.310
		Icodextrin	79.37	143	80.81	1.13		80.00		1.64	1.13	0.175		0.00		
	Week 26	Control	77.66	83	77.99	1.44		78.00		0.33	1.60	0.848		0.00		0.883
		Icodextrin	79.36	130	78.31	1.07		80.00		-1.06	1.34	0.393		0.00		
	Week 39	Control	78.09	70	79.44	1.36		80.00		1.36	1.53	0.377		0.00		0.999
		Icodextrin	79.58	111	80.09	1.30		80.00		0.51	1.33	0.700		0.00		
	Week 52	Control	79.16	62	78.37	1.37		79.00		-0.79	1.77	0.656		0.00		0.602
		Icodextrin	79.09	104	79.81	1.11		80.00		0.72	1.49	0.629		0.00		

@ BASELINE is the Week 0 value.
p W/in= p-value from the within treatment group paired t-test for significant mean change from baseline.
p Betw= Baseline (Week 0): p-value from analysis of variance testing for significant differences across treatment group means.
Post-baseline (Treatment: Wks 2-52): p-value from analysis of covariance testing for significant differences across treatment groups for mean changes.

The difference in systolic blood pressure change from baseline to week 52 (4mmHg mean increase in the Icodextrin group compared to a 2mmHg decrease in the control patients) became an issue. It was thought that Icodextrin might increase systolic pressure, and that was the "smoking gun" to explain an increased mortality risk. They requested that further analyses be done and provided to the agency. Those new systolic blood pressure data analyses follow.

The box plots were presented on the following chart. The number of patients evaluated at each timepoint can be ascertained by consulting the data chart above.

Blood Pressure Box Plots for Each Visit
SYSTOLIC BP (mmHg)



More patients treated with Icodextrin had elevated systolic blood pressure over the course of these evaluations. These patients did not necessarily have bad outcomes. The direction and magnitude of systolic blood pressure change can be better evaluated in the following shift tables. It should be noted that only patients from study 130 who entered study 131 had blood pressure readings at weeks 2 and 4. In study 131 visits were 13 weeks apart. Therefore not only is the database incomplete in numbers of patients captured at each timepoint, but observations of blood pressure were infrequent.

For those alive:

Correlation of BP Shifts By Treatment Group for Each Visit

SYSTOLIC BP

Death= No

				Systolic BP at Visit					
				<120mmHg		120-140mmHg		>140mmHg	
visit	TRT	Systolic BP at Baseline	N	N	Pct	N	Pct	N	Pct
Week 2	Control	<120mmHg	13	11	84.6	2	15.4	-	-
		120-140mmHg	24	3	12.5	11	45.8	10	41.7
		>140mmHg	20	1	5.0	8	40.0	11	55.0
	Icodextrin	<120mmHg	18	12	66.7	5	27.8	1	5.6
		120-140mmHg	18	4	22.2	10	55.6	4	22.2
		>140mmHg	24	-	-	11	45.8	13	54.2
Week 4	Control	<120mmHg	13	10	76.9	3	23.1	-	-
		120-140mmHg	24	10	41.7	9	37.5	5	20.8
		>140mmHg	20	2	10.0	4	20.0	14	70.0
	Icodextrin	<120mmHg	18	7	38.9	8	44.4	3	16.7
		120-140mmHg	18	5	27.8	8	44.4	5	27.8
		>140mmHg	24	2	8.3	7	29.2	15	62.5
Week 13	Control	<120mmHg	15	12	80.0	1	6.7	2	13.3
		120-140mmHg	35	8	22.9	10	28.6	17	48.6
		>140mmHg	36	5	13.9	11	30.6	20	55.6
	Icodextrin	<120mmHg	33	17	51.5	11	33.3	5	15.2
		120-140mmHg	41	6	14.6	23	56.1	12	29.3
		>140mmHg	57	5	8.8	15	26.3	37	64.9
Week 26	Control	<120mmHg	13	9	69.2	3	23.1	1	7.7
		120-140mmHg	31	7	22.6	14	45.2	10	32.3
		>140mmHg	34	3	8.8	12	35.3	19	55.9
	Icodextrin	<120mmHg	31	17	54.8	7	22.6	7	22.6
		120-140mmHg	40	4	10.0	25	62.5	11	27.5

Correlation of BP Shifts By Treatment Group for Each Visit

SYSTOLIC BP

Death= No

				Systolic BP at Visit					
				<120mmHg		120-140mmHg		>140mmHg	
Visit	TRT	Systolic BP at Baseline	N	N	Pct	N	Pct	N	Pct
Week 26	Icodextrin	>140mmHg	53	6	11.3	19	35.8	28	52.8
Week 39	Control	<120mmHg	11	9	81.8	2	18.2	-	-
		120-140mmHg	27	8	29.6	10	37.0	9	33.3
		>140mmHg	29	1	3.4	15	51.7	13	44.8
	Icodextrin	<120mmHg	27	13	48.1	6	22.2	8	29.6
		120-140mmHg	34	9	26.5	16	47.1	9	26.5
		>140mmHg	48	3	6.3	15	31.3	30	62.5
Week 52	Control	<120mmHg	11	6	54.5	3	27.3	2	18.2
		120-140mmHg	25	4	16.0	13	52.0	8	32.0
		>140mmHg	26	3	11.5	10	38.5	13	50.0
	Icodextrin	<120mmHg	26	5	19.2	14	53.8	7	26.9
		120-140mmHg	34	5	14.7	15	44.1	14	41.2
		>140mmHg	44	4	9.1	15	34.1	25	56.8

For those who died:

Correlation of BP Shifts By Treatment Group for Each Visit

SYSTOLIC BP

Death= Yes

				Systolic BP at Visit					
				<120mmHg		120-140mmHg		>140mmHg	
Visit	TRT	Systolic BP at Baseline	N	N	Pct	N	Pct	N	Pct
Week 2	Control	<120mmHg	1	1	100.0	-	-	-	-
		120-140mmHg	4	2	50.0	1	25.0	1	25.0
	Icodextrin	<120mmHg	1	1	100.0	-	-	-	-
		120-140mmHg	4	1	25.0	3	75.0	-	-
		>140mmHg	2	-	-	2	100.0	-	-
Week 4	Control	<120mmHg	1	1	100.0	-	-	-	-
		120-140mmHg	3	1	33.3	-	-	2	66.7
	Icodextrin	<120mmHg	1	-	-	1	100.0	-	-
		120-140mmHg	4	2	50.0	-	-	2	50.0
		>140mmHg	2	-	-	-	-	2	100.0
Week 13	Control	<120mmHg	1	1	100.0	-	-	-	-
		120-140mmHg	5	-	-	3	60.0	2	40.0
		>140mmHg	2	-	-	1	50.0	1	50.0
	Icodextrin	<120mmHg	2	1	50.0	-	-	1	50.0
		120-140mmHg	6	-	-	4	66.7	2	33.3
		>140mmHg	3	-	-	2	66.7	1	33.3
Week 26	Control	120-140mmHg	3	-	-	2	66.7	1	33.3
		>140mmHg	2	2	100.0	-	-	-	-
	Icodextrin	120-140mmHg	4	2	50.0	2	50.0	-	-
		>140mmHg	2	-	-	1	50.0	1	50.0
Week 39	Control	120-140mmHg	2	-	-	1	50.0	1	50.0
		>140mmHg	1	1	100.0	-	-	-	-
	Icodextrin	120-140mmHg	1	-	-	1	100.0	-	-

NOTE: Each Patient Who Died is Counted at Each Visit for Which BP was Measured

Correlation of BP Shifts By Treatment Group for Each Visit

SYSTOLIC BP

Death= Yes

				Systolic BP at Visit					
				<120mmHg		120-140mmHg		>140mmHg	
visit	TRT	Systolic BP at Baseline	N	N	Pct	N	Pct	N	Pct
Week 36	Icodextrin	>140mmHg	1	-	-	1	100.0	-	-

There are shift from the "normal" range to "high" and "low" at various timepoints for both those alive and those who died. No particular pattern of change within or between cohorts is clear. More informative data were provided in the blood pressure readings of those who died.

Those readings were:

Treatment Group	Patient ID	Study Visit Date	Study Day for BP	Systolic BP (mmHg)	Diastolic BP (mmHg)	Systolic BP Change (mmHg)	Diastolic BP Change (mmHg)	Day of Death
Control	01501	19MAY1998	1	144	62	-	-	328
		17AUG1998	91	184	94	40	32	328
		24NOV1998	190	112	74	-32	12	328
		25FEB1999	283	116	64	-28	2	328
	15202	24JUN1998	1	120	82	-	-	177
		08JUL1998	15	112	86	-8	4	177
		23JUL1998	30	110	72	-10	-10	177
	18102	10AUG1998	1	138	81	-	-	160
		24AUG1998	15	151	69	13	-12	160
		08SEP1998	30	115	62	-23	-19	160
		13NOV1998	96	139	61	1	-20	160
	21205	26AUG1998	1	131	62	-	-	223
		09SEP1998	15	131	68	0	6	223
		23SEP1998	29	143	64	12	2	223
		02DEC1998	99	128	65	-3	3	223
		16FEB1999	175	130	68	-1	6	223
	22102	15APR1998	1	140	72	-	-	303
		29APR1998	15	118	82	-22	10	303
		13MAY1998	29	146	72	6	0	303
		21JUL1998	100	144	84	4	12	303
		12OCT1998	181	130	68	-10	-4	303
		14JAN1999	275	126	68	-14	-4	303
	32401	14JAN1999	1	180	84	-	-	359
		16APR1999	93	129	76	-51	-8	359
		22JUL1999	190	116	66	-64	-18	359
		20OCT1999	280	171	101	-9	17	359
	35101	13AUG1998	1	97	68	-	-	113
		27AUG1998	15	97	73	0	5	113
		08SEP1998	27	113	79	16	11	113
		18NOV1998	98	102	53	5	-15	113
	40301	04DEC1998	1	138	52	-	-	395
		29MAR1999	116	160	70	22	18	395
		28MAY1999	176	146	66	8	14	395
		01SEP1999	272	200	92	62	40	395
	43403	08MAR1999	1	131	69	-	-	361
		14JUN1999	99	135	70	4	1	361
Icodextrin	02401	14DEC1998	1	150	70	-	-	176
		15FEB1999	64	100	60	-50	-10	176
	06102	02SEP1998	1	162	100	-	-	78
		17SEP1998	16	136	94	-26	-6	78
		01OCT1998	30	148	100	-14	0	78
	11601	14JAN1999	1	217	96	-	-	138
		23APR1999	100	123	54	-94	-42	138
		26MAY1999	133	100	30	-117	-66	138

Treatment Group	Patient ID	Study Visit Date	Study Day for BP	Systolic BP (mmHg)	Diastolic BP (mmHg)	Systolic BP Change (mmHg)	Diastolic BP Change (mmHg)	Day of Death
Icodextrin	18106	17AUG1998	1	120	61	-	-	148
		31AUG1998	15	115	57	-5	-4	148
		14SEP1998	29	146	77	26	16	148
		16NOV1998	92	142	77	22	16	148
	19503	16FEB1999	1	90	70	-	-	279
		20APR1999	64	118	60	28	-10	279
	22106	04JUN1998	1	130	64	-	-	241
		17JUN1998	14	140	62	10	-2	241
		01JUL1998	28	144	72	14	8	241
		08SEP1998	97	120	82	-10	18	241
		30NOV1998	180	110	70	-20	6	241
	22202	15JUL1998	1	182	94	-	-	324
		29JUL1998	15	122	74	-60	-20	324
		11AUG1998	28	210	110	28	16	324
		12OCT1998	90	122	72	-60	-22	324
		11JAN1999	181	182	92	0	-2	324
		12APR1999	272	122	78	-60	-16	324
	26503	15DEC1998	1	146	87	-	-	23
	27102	10JUL1998	1	104	70	-	-	169
		23JUL1998	14	104	60	0	-10	169
		10AUG1998	32	138	70	34	0	169
		29OCT1998	112	100	70	-4	0	169
	30302	14DEC1998	1	134	60	-	-	164
		19MAR1999	96	158	60	24	0	164
	30501	02DEC1998	1	140	80	-	-	123
		19MAR1999	108	118	70	-22	-10	123
	32301	16FEB1999	1	103	73	-	-	293
		20MAY1999	94	162	100	59	27	293
		22JUN1999	127	132	70	29	-3	293
	35301	16OCT1998	1	168	83	-	-	156
	35401	23NOV1998	1	145	75	-	-	208
		01MAR1999	99	170	81	25	6	208
		27MAY1999	186	138	61	-7	-14	208
	38102	27OCT1998	1	140	70	-	-	256
		10NOV1998	15	120	60	-20	-10	256
		24NOV1998	29	104	60	-36	-10	256
		27JAN1999	93	120	70	-20	0	256
		28APR1999	184	122	80	-18	10	256
		20MAY1999	206	130	80	-10	10	256
	38103	27OCT1998	1	130	80	-	-	364
		12NOV1998	17	130	80	0	0	364
		27NOV1998	32	118	70	-12	-10	364
		27JAN1999	93	120	80	-10	0	364
		29APR1999	185	100	60	-30	-20	364

Two patients died of stroke. Both were Icodextrin treated.
The blood pressure changes from baseline to last measurement were:
Patient 2401 -50mmHg systolic, -10mmHg diastolic
Patient 35401 -7mmHg systolic, -14mmHG diastolic.
Only one patient had a marked increase in systolic pressure from 138mmHg at baseline to 200mmHg at exit. That patient was a control patient. Decrease in systolic pressure was more frequently observed, particularly in the Icodextrin treated patients.
There is no evidence in these data that Icodextrin raised systolic pressure in those who died.
From the data provided, I do not think there is a signal that Icodextrin raised systolic pressure. This conclusion is based both on the incompleteness of the database, and the lack of significant directionality in the blood pressure shifts for those on Icodextrin versus those on control. As noted in the original medical review, more hypotension was noted in Icodextrin treated patients compared to control.

PROPOSED LABELING CHANGES

Labeling recommendations were made by FDA chemistry, biopharmaceutics and medical reviewers. Some were implemented by the sponsor. The chemist and biopharmaceutics reviewers will consider whether the sponsor has adequately addressed their concerns.

Concerning the medical portion changes:

Without the changes noted above, I do not think the proposed labeling is acceptable.

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/

Stephan Fredd
9/21/01 01:48:35 PM
MEDICAL OFFICER

To: NDA 21321
From: Stephen Fredd, M..D.
Subject: Amendment dated 8/29/01

On 8/29/01 the sponsor submitted a corrected analysis of study RD-97-CA-131involving the number of patients and deaths in the CAPD and APD subgroups. This was necessitated by the fact that the sponsor found an error in the program used to provide the original subgroup analyses.
To provide some context for these reanalyses, the study was a 52 week randomized, double-blind prospective safety study in 287 ESRD patients undergoing CAPD or APD. The primary endpoints were safety endpoints including mortality rates, changes in membrane transport characteristics, adverse reactions. laboratory abnormalities, clinical signs such as edema.
The sponsor provided a variety of analyses of the mortality result.
Their survival analysis indicating days to death or censoring was:

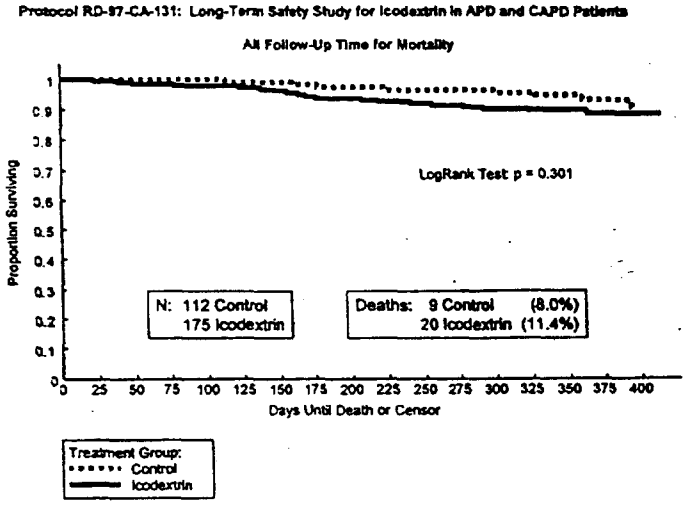


Table 1: Mortality Analysis Including Additional Follow-up Data
Based on Survival Times in Days -- Survivors Have Censored Times

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

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

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

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

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

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

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

These results were not involved in the software problem used to analyze APD and CAPD subsets, and remain the same.

Since there was some numerical difference in mortality rates suggesting a possible increased risk with Icodextrin, numerous subgroup analyses were done. There were 4 prespecified randomized strata: 1) APD/2L, APD/2.5L, CAPD/2L, and CAPD/2/5L.
In the original report the following data were provided.

APD MORTALITY

The mortality rates with 90%CIs were:

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

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

For the APD/2L stratum;

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

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

For the APD/2.5L stratum:

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

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

CAPD MORTALITY

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

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

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

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

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

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

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

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

The full report of the study is contained in the medical review dated 6/8/01.

NEW ANALYSES

In this amendment the total number of patients for the study, assignment to treatment and number of deaths remain the same, but for the CAPD and APD subgroups the number change slightly.

CAPD (Section 12.11.2)**	Original Report			Amendment C		
	Total n	Control n,%	Icodextrin n(%)	Total n	Control n(%)	Icodextrin n(%)
ITT Population	210	76	134	210	91	119
W/D* due to Transplant	16	6, 7.9%	10, 7.5%	15	7, 7.7%	8, 6.7%
WD due to AE	45	20, 26.3%	25, 18.7%	43	24, 26.4%	19, 16%
WD due to death	7	2, 2.6%	5, 3.7%	10	4, 4.4%	6, 5%
WD due to Prot. Dev. Or Other	23	7, 9.2%	16, 11.9%	16	4, 4.4%	12, 10.1%
CAPD 2.0L (Sect. 12.11.3)						
ITT population using 2.0L	109	34	75	111	45	66
CAPD 2.5L (Sect. 12.11.4)						
ITT population using 2.5L	101	42	59	99	46	53

* WD = Withdrawal **Report Section

APD(Section 12.11.5)	Original Report			Amendment C		
	Total n	Control n,%	Icodextrin n,%	Total n	Control n,%	Icodextrin n,%
ITT Population	77	36	41	77	21	56
W/D due to Transplant	5	4, 11.1%	1, 2.4%	6	3, 14.3%	3, 5.4%
WD due to AE	12	6, 16.7%	6, 14.6%	17	3, 14.3%	14, 25%
WD due to death	4	2, 5.6%	2, 4.9%	1	0	1, 1.8%
WD due to Protocol Dev. Or Other	6*	2, 5.6%	4, 9.8%	10	4, %	6, 3.6%
CAPD 2.0L (Sect. 12.11.3)						
ITT population using 2.0L	53	23	30	51	12	39
CAPD 2.5L (Sect. 12.11.4)						
ITT population using 2.5L	24	13	11	26	9	17

* WD = Withdrawal **Report Section

The corrected mortality data for the APD subgroup were:

Mortality Analysis Including Additional Follow-up Data
Based on Survival Times in Days -- Survivors Have Censored Times
Stratum 3 and 4 - All APD Patients

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	21	1	4.8	N/A	N/A	N/A	328.0 #	.	.	.	0.408
Icodextrin	56	6	10.7	N/A	N/A	N/A	262.2 #	8.48	248.2	276.1	
TOTALS	77	7	9.1	N/A	N/A	N/A	311.9 #	7.57	299.5	324.4	

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

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	21	261.4	1	0.004	0.000	0.106	0.05	0.00	1.27
Icodextrin	56	642.9	6	0.009	0.000	0.168	0.11	0.00	2.02

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

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

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

Icodextrin Mean	Control Mean	Difference (Ico - Ctrl)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Ctrl)	Lower 90%	Upper 90%
0.009	0.004	0.006	0.0054	-0.003	0.014	0.066	-0.041	0.173

For the APD/2L subgroup the new results were:

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	12	146.6	1	0.007	0.000	0.143	0.08	0.00	1.71
Icodextrin	39	460.2	3	0.007	0.000	0.139	0.08	0.00	1.67

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

For the APD/2.5L subgroup:

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	9	114.8	0	0.000	0.000	0.008	0.00	0.00	0.00
Icodextrin	17	182.7	3	0.016	0.000	0.227	0.20	0.00	2.73

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

The new APD mortality result, 1/21(4.8%) for control and 6/56(10.7%) for Icodextrin, is somewhat different than the original report of 4/36(11%) and 5/41(12%), but what change occurred mainly effected the control result. With these small numbers, further subgroup analysis of 2L and 2.5L is difficult to interpret.

For The CAPD group the new results were:

Mortality Analysis Including Additional Follow-up Data
Based on Survival Times in Days – Survivors Have Censored Times
Stratum 1 and 2 - All CAPD Patients

Treatment Group	Number Patients	Number Deaths	Percent Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	91	8	8.8	N/A	N/A	N/A	383.2 #	5.39	374.3	392.1	0.426
Icodextrin	119	14	11.8	N/A	N/A	N/A	346.6 #	5.35	337.8	355.4	
TOTALS	210	22	10.5	N/A	N/A	N/A	377.9 #	4.12	371.1	384.7	

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

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	91	1094.7	8	0.007	0.000	0.148	0.09	0.00	1.78
Icodextrin	119	1366.7	14	0.010	0.000	0.177	0.12	0.00	2.12

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

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

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

Icodextrin Mean	Control Mean	Difference (Ico - Ctrl)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ico - Ctrl)	Lower 90%	Upper 90%
0.010	0.007	0.003	0.0038	-0.003	0.009	0.035	-0.039	0.110

For the CAPD/2L subgroup, the new results were:

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	45	538.9	4	0.007	0.000	0.149	0.09	0.00	1.79
Icodextrin	66	742.2	10	0.013	0.000	0.204	0.16	0.00	2.45

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

For the CAPD 2.5L subgroup:

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

Treatment Group	Number Patients	Total Months	Number Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	46	555.8	4	0.007	0.000	0.147	0.09	0.00	1.76
Icodextrin	53	624.6	4	0.006	0.000	0.138	0.08	0.00	1.66

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

The new results do not differ much from the original report in percentages of patients who died in control and Icodextrin. The original report stated that there were 5/76(6.6%) deaths in control patients and 15 134(11.1%) in Icodextrin treated patients. The new report states that there were 8/91(8.8%) deaths in control patients and 14/119(11.8%) in Icodextrin treated patients. Further analysis of the 2L and 2.5L subgroups does not show much difference between groups.
The new results for the APD and CAPD subgroups do not reveal much difference in mortality rate between those cohorts.

The sponsor provided a listing of the patients who died by APD or CPD as follows:

	RX	Center	Pt.#	Days in study	Days to death	Cause of Death
APD	Control	39	1501	289	328	UNKNOWN
	Icodextrin	10	19503	64	279	CARDIAC
		9	26503	15	23	Sepsis and metabolic acidosis as a consequences of retroperitoneal gangrene and peritonitis following renal transplant
		55	30501	108	123	Heart Attack
		56	45401	15	39	Cardiac Arrest
		44	61603	69	219	CARDIAC ARREST, CAUSE UNKNOWN
		93	62501	49	49	Myocardial Infarction
CAPD	Control	35	15202	53	177	UNKNOWN
		17	18102	160	160	Cardiac Arrest
		20	21205	223	223	Cardiac Arrest
		25	22102	303	303	Acute Necrotizing Bronchopneumonia
		124	32401	274	359	CARDIAC ARREST, CAUSE UNKNOWN
		121	35101	113	113	Myocardial Infarction
		126	40301	367	395	Pneumonia and Heart Failure
		58	43403	138	361	MULTI SYSTEM ORGAN FAILURE
	Icodextrin	11	2401	52	176	CEREBROVASCULAR ACCIDENT INCLUDING INTRACRANIAL HEMORRHAGE
		22	6102	78	78	Electro-mechanical Dissociation
		53	11601	133	138	Heart Arrest
		17	18106	148	148	Cardiac Arrest
		25	22106	226	241	Myocardial Infarction
		25	22202	324	324	Myocardial Infarction
		52	27102	169	169	Acute Cardiac Arrest
		55	30302	164	164	Natural Causes (exact unknown)
		124	32301	108	293	WITHDREW FROM DIALYSIS D/T ESCALATION OF SEVERE PERIPHERAL VASCULAR DISEASE, DIABETES MELLITUS - 20-NOV-1999
		121	35301	91	156	RENAL FAILURE
		121	35401	206	208	Cerebrovascular Accident
		57	38102	206	256	END STAGE RENAL DISEASE
		57	38103	254	364	PERIPHERAL VASCULAR DISEASE PER DEATH CERTIFICATE. END STAGE RENAL DISEASE (L) ABOVE KNEE AMPUTATION.
		47	42302	363	363	Bowel Infarct post Myocardial Infarction

COMMENTS

The corrected data does not indicate that APD or CAPD are particular risk factors for death when Icodextrin is used for peritoneal dialysis. The numerical difference in the new mortality result for the APD group compared to the original result is the biggest change, and mainly due to a different finding in the control group. The mortality rate in the APD Icodextrin group remains similar to that of the CAPD Icodextrin treated patients. Further subsetting of these data re 2L and 2.5L groups is not informative. Since the reason for these corrected number was a problem with the program used originally, I asked the sponsor whether all other programs used for analysis had been checked. They replied that all had been checked, and the originally submitted results are accurate.

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

/s/

Stephan Fredd
9/7/01 01:33:09 PM
MEDICAL OFFICER

RHPM NDA Overview Update
November 5, 2002

NDA 21-321	Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution
Sponsor:	Baxter Healthcare Corporation
Classification:	1S
Date of Application:	December 22, 2000
Date of Receipt:	December 22, 2000
Date of FPL Submission:	November 6, 2002
Date of FPL Receipt:	November 7, 2002
User Fee Goal Date:	January 6, 2003

This NDA received an Approvable letter on October 22, 2001. Manufacturing deficiencies noted in the Approvable Letter were resolved in September of 2002.

At a Pre-Approval Safety Conference on September 27, 2002, concerns relating the relating to falsely elevated glucose levels and a [redacted] impurity issue related to a recall of the drug in Europe were discussed. On October 4, 2002 Baxter representatives met with the Agency to discuss the concerns identified at the Pre-Approval Safety Conference. On October 11, 2002 a Teleconference between the Division and Baxter was held to review Baxter's proposed response to the Agency's concerns.

Baxter submitted new labeling to respond to the Agency's concerns on October 15 and 28, 2002. At an internal Agency meeting on October 31, 2002, it was decided that Baxter had responded sufficiently to the Agency's safety concerns. During a November 5, 2002 Teleconference, minor changes to the most recently submitted (October 28, 2002) labeling were discussed, along with other requirements (post-marketing safety commitments) related to approval of Extraneal. Baxter agreed to the labeling changes and post-marketing safety commitments and submitted FPL on November 6, 2002. During review of the FPL submission, a minor editorial error (a missing comma) was noted. Baxter has agreed to correct the error on the next printing.

Russell Fortney
Regulatory Health Project Manager

rf/12-2-02

RHPM NDA Overview
October 10, 2001

NDA 21-321	Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution
Sponsor:	Baxter Healthcare Corporation
Classification:	1S
Date of Application:	December 22, 2000
Date of Receipt:	December 22, 2000
User Fee Goal Dates:	October 22, 2001 (primary) December 22, 2001 (secondary)

Background

Baxter Healthcare Corporation submitted this NDA for Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution for the treatment of chronic renal failure on December 22, 2000. The related IND is [redacted] Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution received Orphan Drug Designation 97-1056 on July 18, 1997.

Extraneal was presented to the Cardiovascular and Renal Drugs Advisory Committee on August 9, 2001. The Committee recommended 10-yes to 0-no that Extraneal was an effective dialysis drug and that it should be approved for marketing as an alternative dialysis solution. The Committee indicated that the data did not demonstrate superiority of this dialysate over currently marketed products. Post-marketing studies should provide additional data on the effects of Extraneal on blood viscosity, blood pressure elevations and cardiovascular mortality.

Review

Postmarketing Commitments:	Per an October 9, 2001 discussion with Dr. Lipicky, he stated that postmarketing commitments were not necessary.
Safety Update:	Per the sponsor, the safety update is "To be filed as required." The sponsor is awaiting the action letter before they submit the Safety Update.
Patent info:	Included in package
Exclusivity:	Included in package. Pursuant to 21 CFR 314.31 and 316.31, the sponsor claims seven (7) years exclusivity for the proposed indication.
Pediatric info:	Waiver granted. The sponsor requested a waiver from pediatric use information, in accordance with 21 CFR 314.55 (d). The requirement for pediatric use information has been waived because the drug has been granted orphan drug status.

DSI: In conjunction with the Division, DSI inspected three (3) sites among the following studies:

- Protocol #RD-97-CA-130, "A study to evaluate the safety and efficacy of a 7.5% Solution of Icodextrin Peritoneal Dialysis Solution in patients treated with continuous peritoneal (CAPD) dialysis"

- Protocol #RD-97-CA-131, "A study to evaluate the safety of a 7.5% Solution of Icodextrin Peritoneal Dialysis Solution in patients treated with peritoneal dialysis in North America"

No major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable.

Debarment Certification: Included in package

OPDRA Tradename Review: OPDRA had no objections to the use of the proprietary name, Extraneal, on initial review. Labeling revisions were recommended to minimize potential user error (see OPDRA's 7-16-01 initial review). A re-review of the trade name is pending as of 10-10-01.

Medical Review

Reviewer: Stephen Fredd, M.D.

Labeling: See Dr. Fredd's 6-8-01 review and 9-21-01 amendment for labeling recommendations.

Conclusion: Considering the safety and efficacy data, a recommendation for approval for those patients inadequately responding to CAPD or APD with Dextrose for the long-dwell period is made. A post-marketing, long term, active-controlled, randomized mortality study should be considered. (see Dr. Fredd's 6-8-01 review and 9-7-01 and 9-21-01 amendments).

Statistical Review

Reviewer: John Lawrence, Ph.D.

Labeling: None

Conclusion: Since the mortality status of over half (161/289) of the patients was not known 375 days from the start of the study, this reviewer doubts that the questions raised by the Advisory Committee can be answered from the data provided. The data provided seems to indicate that there is insufficient evidence to rule out the equality of the two survival curves. Numerically, the estimated hazard ratio for mortality in the Extraneal group relative to the control group was 1.51 with a 95% confidence interval of (0.686, 3.30). Moreover, the rate of loss to follow-up in the last month is high and the Extraneal group has more patients lost to follow-up. This might induce bias in favor of the Extraneal group. Hence, the excess risk could be much higher than observed (see Dr. Lawrence's 4-23-01 review).

The sponsor submitted a new data set that contains the correct number of days of survival for each patient. Using this new data set, this reviewer found that the proportion of patients in both groups with known survival status at least 390 days after randomization is over 90% (see Dr. Lawrence's 8-1-01 amendment).

Chemistry Review

Reviewer:	Ram Mittal, Ph.D.
Labeling:	See Dr. Mittal's 9-10-01 and 9-26-01 reviews for labeling recommendations.
Conclusion:	As noted in Review #1, the Office of Compliance (OC) had issued a WITHHOLD overall recommendation (July 16, 2001). EER status of one facility is still WITHHOLD. All CMC review issues have been resolved. Ms. P. Alcock from Office of Compliance was contacted on September 25, 2001 to inquire if there were any further developments regarding cGMP status of the facility. She stated that cGMP problems were major and that OC continues to recommend WITHHOLD. Based on this, the NDA is NOT APPROVABLE from the Chemistry, Manufacturing and Controls standpoint (see Dr. Mittal's 9-10-01 and 9-26-01 reviews).

Pharmacology Review

Reviewer:	James Willard, Ph.D.
Labeling:	See Dr. Willard's 8-13-01 review for labeling recommendations.
Conclusion:	Dr. Willard states that he "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." (see Dr. Willard's 8-13-01 review)

Biopharmaceutics Review

Reviewer:	Elena Mishina, Ph.D.
Labeling:	See Dr. Mishina's 7-12-01 review for labeling recommendations.
Conclusion:	1) The assay used by the sponsor to measure the total icodextrin concentrations in all matrixes is lacking specificity. Quality control samples are not provided in each of the submitted studies. Therefore, it is impossible to evaluate the precision and accuracy of the assay methods used by the sponsor. 2) Icodextrin and its metabolites concentrations are measured in plasma, urine and spent dialysate in the studies after the single 12 hours dwell and at steady state. Icodextrin pharmacokinetics profiles in the peritoneal cavity decline with zero-order rate constant. The model proposed by the sponsor to describe plasma kinetics of total icodextrin is not reliable due to the lack of assay specificity and measurements referring to the sum of glucose polymers. Thus the calculated parameters for total icodextrin should not be included in the Package Insert. 3) The sponsor did not make an attempt to describe the pharmacokinetic characteristics of icodextrin metabolites. 4) Net absorption of icodextrin to the systemic circulation after the single 12 hours dwell and during the chronic automated PD procedures was similar, about 40%. Peak plasma total icodextrin and its degradation products concentrations were between 4 and 6 g/L through all studies. Therefore, the sponsor properly concluded that the duration and mode of

PD procedures do not influence the systemic exposure to total icodextrin. (See Dr. Mishina's 7-12-01 review.)
The revised draft of the Package Insert for Extraneal is acceptable from the point of view of the Office of Clinical Pharmacology ad Biopharmaceutics. (See Dr. Mishina's 9-24-01 review.)

Microbiology Review

Reviewer:	Vivian Greenman, Ph.D.
Labeling:	None
Conclusion:	Recommend approval of the NDA for sterility assurance of the subject drug (see Dr. Greenman's 7-12-01 review).

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

qn/10-10-01

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

/s/

Quynh Nguyen
10/12/01 09:51:41 AM
CSO

Teleconference Minutes

Date:	November 5, 2002
Sponsor:	Baxter Healthcare Corporation
Application:	NDA 21-321, Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution
Subject:	Labeling Changes Related to Glucose Monitoring Issue
FDA Attendees:	Douglas C. Throckmorton, M.D. Director, Cardio-Renal Drug Products, HFD-110 Russell Fortney, Regulatory Health Project Manager, HFD-110
Baxter Attendees:	Lisa Skeens, Ph.D., Director, Regulatory Affairs

Background:

A Pre-Approval Safety Conference was held on September 27, 2002. At this meeting, safety issues relating to falsely elevated glucose readings were discussed. Baxter responded to the Agency's concerns at a meeting on October 4, 2002. During an October 11, 2002 Teleconference with the Division, Baxter received additional feedback on their changes. In response, Baxter submitted updated labeling on October 15 & 28, 2002. Another internal meeting was held on October 31, 2002, with Dr. Temple in attendance, to review these changes. It was agreed that the changes were acceptable, with a few minor editorial changes. This teleconference was arranged to discuss the required changes with Baxter, and to also discuss additional requirements related to the test-strip issue.

Teleconference:

Dr. Throckmorton began by indicating that Baxter's most recent labeling submission (dated October 28, 2002) was acceptable, and that no black box would be required. We discussed the following required minor editorial changes:

1. Under **CLINICAL STUDIES/Ultrafiltration, Urea and Creatinine Clearance**, the first line should be changed from:

   /

   to:

   "In the active-controlled trials of one to six months in duration, described below, EXTRANEAL used once-daily for"

2. Under **WARNINGS**, the first sentence of the second paragraph should be changed from:

   /

   to:

"Blood glucose measurement must be done with a glucose-specific method (monitor and test strips) to avoid interference with maltose, released from EXTRANEAL."

3. Under PATIENT INFORMATION, (page 15, lines 1-3) in the second sentence of the paragraph that begins with "If you monitor your blood glucose..." the word "uses" should be changed to "use".

Baxter is to submit Final Printed Labeling with the above changes. Dr. Throckmorton said that Baxter's proposed PPI was acceptable.

Dr. Throckmorton also informed the Sponsor of the following expectations related to approval of Extraneal:

- Baxter will communicate with the various test strip and monitor manufacturers regarding the possible interaction with Extraneal to insure that they are aware of the situation if/when patients call.
- Baxter will initiate a patient patient survey (or some similar mechanism) to insure that patients are not encountering problems obtaining information from the manufacturers.
- Baxter will address the issue of how to inform Hospital Emergency Room medical staff about the possible interaction of Extraneal with non-glucose specific test strips.
- All adverse events related to hypoglycemia, for at least the first year, will be reported as 15-Day Reports.

The above issues will also be communicated in the action letter. Baxter is not required to address them prior to issuance of the letter.

Minutes Preparation: /S/ 11.5.02
Russell Fortney

Concurrence, Chair /S/ 11.5.02
Douglas C. Throckmorton, M.D.

drafted rf-11/5/02
finalized rf-11/5/02

reviewed: Dthrockmorton-11/5/02

********** -COMM. JOURNAL- ********** DATE NOV-05-2002 ***** TIME 11:19 ********

MODE = MEMORY TRANSMISSION START=NOV-05 11:18 END=NOV-05 11:19

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********** -CARDIO RENAL - ***** - 301 594 5494- **********

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Rockville, MD 20852

Transmitted to FAX Number:	847-473-6952
Attention:	Dr. Lisa Skeens
Company Name:	Baxter Healthcare Corporation
Phone:	847-473-6558
Subject:	**Minutes**
Date:	November 5, 2002
Pages including this sheet:	**3**
From:	**Russell Fortney**
Phone:	**301-594-5311**
Fax:	**301-594-5494**

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Rockville, MD 20852

Transmitted to FAX Number:	847-473-6952
Attention:	Dr. Lisa Skeens
Company Name:	Baxter Healthcare Corporation
Phone:	847-473-6558
Subject:	**Minutes**
Date:	November 5, 2002
Pages including this sheet:	**3**
From:	**Russell Fortney**
Phone:	**301-594-5311**
Fax:	**301-594-5494**

Minutes of a Teleconference
October 11, 2002

Application:	NDA 21-321 Extraneal (icodextrin)
Sponsor:	Baxter Healthcare Corporation
Subject:	Baxter's Response to Pre-Approval Safety Conference

Attending:

Baxter

Mary Kay Rybicki	Associate Director, Regulatory Affairs

FDA:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Officer Team Leader, HFD-110
Edward Fromm	Regulatory Health Project Manager, HFD-110
Russell Fortney	Regulatory Health Project Manager, HFD-110

Background: On September 27, 2002 a Pre-Approval Safety Conference for NDA 21-321 (Extraneal) was held. The two important points of discussion were:

1. Enzymatic glucose interference by icodextrin metabolites
2. Cloudy effluent/aseptic peritonitis

A subsequent meeting between Baxter and the Agency was held on October 4, 2002 to allow Baxter to discuss and respond to the above concerns as well as a regulatory specification for the [redacted] impurity associated with the recall of the product in Europe. Baxter agreed to formally submit a response to these concerns. This teleconference was arranged to give Baxter some further guidance for their response.

Teleconference: Dr. Throckmorton began by stating that this teleconference would be advisory in nature and the Sponsor should not interpret any discussions to be the Division's final approval on the matters discussed. The Sponsor agreed, and asked only for feedback on their prospective response.

Dr. Throckmorton asked that any future labeling changes be submitted in marked up format so that the Division may follow all proposed changes. Such a version should start with the initial labeling sent with the Approvable letter.

Dr. Throckmorton said that the proposed changes to the **WARNINGS** section of the labeling seem adequate, but added that the Office of Drug Safety may not agree. Dr. Throckmorton also advised that the Sponsor should include in their submission a response to the Division's suggestion of the possibility of a black-box warning for their labeling. The Division would also like to see an alternative to the proposed 800 number, should they decide against including the 800 number in the labeling. The Sponsor agreed to include these areas of discussion in their response.

Dr. Throckmorton asked that information regarding the clinical consequences of falsely elevated glucose readings be included in the Patient Package Insert so that it could be understood by the patients.

The Sponsor asked if they should send a separate amendment for the Chemistry items (impurity) that require attention. Dr. Throckmorton agreed that that would be a good idea.

The Sponsor has indicated that their response to the Agency's questions will be submitted next week. The next internal Agency meeting is scheduled for October 31, 2002. It was agreed that the Sponsor would be available by phone should any questions arise at that meeting.

Signature, Minutes Preparer /S/ 10-15-02 Russell Fortney

Concurrence, Meeting Chair /S/ 10.18.02 Douglas C. Throckmorton, M.D.

Drafted: 10/11/02 Finaled: 10/15/02
rf

rd:
Throckmorton 10/11/02
Stockbridge 10/15/02
Fromm 10/15/02

MESSAGE CONFIRMATION

11/16/01 17:46
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1451 Rockville Pike
Rockville, MD 20852

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

Attention: **Ms. Mary Kay Rybicki**

Company Name: **Baxter Healthcare Corporation**

Phone: (847) 473-6361

Subject: **FDA Participants,**
November 9, 2001 Teleconference

Date: **November 16, 2001**

Pages including this sheet: **2**

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, R.Ph., Safety Evaluator, DDRE I, OPDRA, HFD-430
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Proposed Draft Labeling

Following the November 9, 2001 teleconference, Baxter Healthcare Corporation provided the following labeling proposals via Fax and E-mail:

November 13, 2001 – Fax of Clinical Studies and Laboratory Tests – Serum Electrolytes sections

November 14, 2001- Fax of Entire proposed labeling including changes to Serum Electrolytes section as discussed via telephone with Dr. Throckmorton on November 14, 2001

November 19, 2001 – E-mail to Dr. Throckmorton describing changes to patient numbers in serum Electrolyte section.

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

Minutes of a between Baxter Healthcare and the FDA Division of Cardio-Renal Drug Products

Date: October 4, 2002

Application: NDA 21-321, Extraneal (idocdextrin) Peritoneal Dialysis Solution

Applicant: Baxter Healthcare Co.

Subject: Discuss Safety-Related Labeling Changes

FDA participants

Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Susan Lu. Pharm.D., HFD-430, Team Leader, Office of Drug Safety
Cindy Kortepeter, Pharm.D., HFD-430, Safety Evaluator, Office of Drug Safety
Carol Pamer, HFD-430, Safety Evaluator, Office of Drug Safety
Salma Koessel, M.D., Ph.D., HFD-110, Medical Officer
Andy Haffer, Pharm.D., HFD-42, Division of Drug Marketing, Advertising, and Communications
James Willard, Ph.D., HFD-110, Pharmacologist
Ram Mittal, Ph.D., HFD-810, Chemist
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Sandra Birdsong, HFD-430, Regulatory Health Project Coordinator
Edward Fromm, HFD-110, Regulatory Health Project Manager

Baxter Healthcare

Marsha Wolfson. M.D., Vice President, Global Clinical Affairs
Leo Martis. Ph.D., Vice President, Solutions Development
Mary Kay Rybicki. M.S., Associate Director, Regulatory Affairs

Background

Extraneal (icodextrin) peritoneal dialysis solution was issued an approvable letter on October 22, 2001. A condition of the approvable letter was that a satisfactory inspection of the manufacturing facilities be completed. On September 10, 2002, the Office of Compliance issued an "Acceptable Recommendation" for the manufacturing facilities.

Final printed labeling was submitted on August 29, 2002 and a pre-approval safety conference was held for this new molecular entity on September 27, 2002. Several safety-related concerns were identified at this meeting among them falsely elevated glucose levels depending on the type of glucometer or the type of test used and the need for regulatory specifications for [redacted] impurity associated with the recall of the drug in Europe. The meeting today is to discuss these and other safety-related concerns with the drug identified at the pre-approval safety conference.

Meeting

Dr. Stockbridge opened the meeting by noting that we have identified two safety related concerns with icodextrin that have to be resolved before the product can be approved for marketing:

Impurity

Baxter noted that the product was recalled in Europe in May of this year due to increased customer complaints about a cloudy effluent. This effluent was associated with — byproducts produced by the bacterium *Bacillus acidocaldarius* during the manufacturing process. The sponsor stressed that the high levels (in some batches) were only associated with the — and not the ML Laboratory supplier for the United States. They also noted that the ML facility uses a filtration method that — Nevertheless, the sponsor said they would be conducting a study of the ML plant to see if there was any microbiological contamination and — resulting from the manufacturing process. Dr. Mittal suggested that to prove the capability of the ML process of filtration — a study should be conducted by — The sponsor agreed to this suggestion.

Dr. Stockbridge asked if the — had been tested for a No Effect limit in animals. Baxter replied that they had looked at the inflammatory response in rats and had found a No Effect limit of <10 ng/ml. Based on this information the sponsor has used — both in the United States and in Europe until their investigation has been completed. The sponsor noted that the — was used because that is the current limit of detection for the impurity. They added that complaints have decreased since the new release rates have been instituted. Dr. Stockbridge noted that it would be helpful to submit the No Effect study data in rats to the Division for review. Dr. Willard noted that no protocol had been submitted prior to the studies for review by Pharmacology/Toxicology.

Dr. Stockbridge asked what the levels of — were in the batches that were the subject of complaints in Europe. Baxter referred to Appendix 5 of their briefing book to point out how different batches of drug solution corresponded to consumer complaints. In general, higher levels of — were associated with more product complaints. Dr. Stockbridge and Dr. Karkowsky noted that the data showing the number of complaints related to lots and the size of batches should be more detailed and the sponsor should calculate the number of sterile peritonitis events, normalized to the size of lots that were produced.

Dr. Srinivasachar asked if — were being monitored in the drug substance icodextrin. Baxter said they have considered doing this, but after consultation with European Regulatory authorities decided that the final product would likely have the — impurity in greater amounts.

Dr. Mittal asked that a specification table and a new methods validation package be sent in for the — impurity. Dr. Srinivasachar added that a change in the specifications after approval would have to be submitted as a supplement to the NDA. The sponsor said they would send in the information requested shortly.

Glucose Test Monitoring

Dr. Stockbridge said that because some glucose test strips can overestimate glucose values in the presence of icodextrin, the Agency was considering a black box warning to patients and health care providers. Baxter noted that the average length of time for patients to receive PD solution is about 2 years and that they have received very few reports from patients complaining of hypoglycemia; however, when the event does occur, it is potentially serious. Dr. Haffer said that there might be underreporting of this event because hypoglycemia is frequently attributed to other causes.

Baxter noted that they have an extensive training program for both patients and healthcare professionals and that the package insert is probably not the best mechanism for communicating important warnings about the drug product. They said that it would be their preference to strengthen the warnings in the patient package insert and training materials. Dr. Stockbridge said he was concerned that even with increased training whether health providers would be appropriately sensitized to the risk involved. In addition, an informal survey done by the

Agency's safety evaluators has found that glucose test strips vary among manufacturers and therefore patients may choose a strip that is incompatible with the maltose byproduct of icodextrin. For this reason, it may be helpful to include a 1-800 number for Baxter in the black box warning for patients and healthcare providers to call in case questions arise about what strip to use. Baxter said that they have various 1-800 numbers already in place and said that is their preference (and current practice) to refer patients questions directly to the dialysis healthcare providers.

Dr. Kortepeter noted that there are numerous inconsistencies with the labeling regarding whether the test strip is glucose-specific and whether the device used is a portable monitoring device (glucometer) or one used by a commercial laboratory. In addition, it is unclear in the labeling whether the interference lies with the test strips or the monitor itself. For example, the second sentence under **WARNINGS** states that "Blood glucose measurement must be done with a glucose-specific method to avoid interference by maltose." Dr. Kortepeter suggested that "glucose-specific" be clarified to " ——— " and also whether the test causes interference with a home monitor, a laboratory specific device, or the test strips. She said that the sponsor should try to clarify other instances such as these throughout the labeling which are confusing and inconsistent. Dr. Stockbridge added that the sponsor should also submit arguments as to why a black box warning should or should not be included in the labeling.

Baxter said they would clarify the labeling and patient training materials to be more consistent and would submit these changes shortly for the Agency's review. They asked if these changes could be instituted at the next printing of the labeling. Dr. Stockbridge said the changes submitted would have to be reviewed by those present here today as well as Drs. Temple and Throckmorton and therefore he could not give a definitive answer.

Baxter asked that after the data asked for today have been submitted, how soon would it be before the Agency issues an action on the application. Dr. Stockbridge replied that an internal meeting would be scheduled with Dr. Temple and the review team to look over the materials submitted by the sponsor. After this meeting, which hopefully would take place in the next few weeks, the sponsor would be notified if new final printed labeling was needed or whether the changes to the labeling could be made at the next printing.

Summary of Main Action Items

- Baxter said they are undertaking a study at the United States supplier of the drug to make sure there is no microbial contamination during the manufacturing process. They said that they remain committed to a target release rate of ——— both here and in Europe. The sponsor will send a new validation package and table of specifications for the drug product.

- Baxter will submit a study that tested the No Effect dose of — in rats.

- Baxter will submit a more detailed analysis of consumer complaints versus the size of the batches of drug product. This analysis should be expressed as a graph.

- Baxter will submit changes to the labeling and training materials that strengthen the warning about the potential interference of icodextrin with some glucose test strips. The Agency will hold an internal meeting to review the materials submitted by the sponsor and may ask for revised final printed labeling or permit the changes to be made at the next printing.

Minutes Preparation:

/S/

Edward Fromm

Concurrence, Chair:

/S/ 10/23/02

Norman Stockbridge, M.D., Ph.D.

drafted/ef: 10/9/02/10/23/02

Rd: SBirdsong-10/9/02
RMittal-10/9/02
KSrinivasachar-10/9/02
JWillard-10/9/02
AHaffer-10/9/02
SKoessel-10/20/02
CKortepeter-10/21/02
CPamer-10/21/02
SLu-10/21/02
AKarkowsky-10/22/02

********** -COMM. JOURNAL- ********** DATE OCT-23-2002 ***** TIME 13:13 *********

MODE = MEMORY TRANSMISSION START=OCT-23 13:11 END=OCT-23 13:13

FILE NO.=320

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-FDA,CDER,OND,ODE1,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Woodmont II
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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:	Minutes of Meeting w/FDA, October 4, 2002
Date:	Oct 23, 2002
Pages including this sheet:	4
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

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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:	**Minutes of Teleconference, November 9, 2001**
Date:	**November 29, 2001**
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From:	**Quynh Nguyen, Pharm.D.**
Phone:	**(301) 594-5311**
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Please notify us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes).

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Company Name: **Baxter Healthcare Corporation**

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

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Pages including this sheet: **20**

From: **Qunah Nguyen, Pharm.D.**