CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Chemistry Review(s)

NDA 21-321

Extraneal
Peritoneal Dialysis Solution

Baxter Health Care Corporation

Ramsharan D. Mittal
Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. NDA 21-321

2. REVIEW #: 3

3. REVIEW DATE: 11-DEC-2002

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	20-DEC-00
N-BZ	20-MAR-01
N-BZ	16-MAY-01
N-BZ	23-MAY-01
BL	13-JUN-01
N-BZ Amendment	19-SEP-01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-BC Amendment	26-DEC-01
N-BC Amendment	23-JAN-02
N-BC Amendment	28-FEB-02
N-BC Amendment	21-MAR-02
N-BC Amendment	04-APR-02
N 000(C)	18-APR-02
N 000(C)	25-APR-02
N 000(C)	13-MAY-02
N 000(C)	22-MAY-02
N 000(C)	28-JUN-02
N 000(C)	11-JUL-02
N 000(C)	30-JUL-02
N 000(C)	31-JUL-02
N 000(C)	11-SEP-02
N 000(C)	15-OCT-02
N 000(C)	28-OCT-02

7. **NAME & ADDRESS OF APPLICANT:**

Name: Baxter Health care Corporation
Address: 1620 Waukegan Road
McGaw Park, IL 60885

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Extraneal
b) Non-Proprietary Name (USAN): Icodextrin
c) Code Name Dextrin 20 and Polyglucose
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Chronic Renal Failure

11. DOSAGE FORM: Peritoneal Dialysis Solution

12. STRENGTH/POTENCY 7.5%w/v

13. ROUTE OF ADMINISTRATION: Intraperitoneal

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

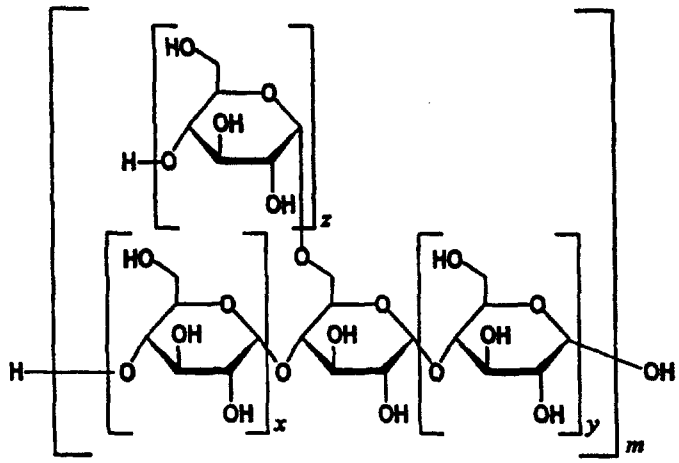
16. CHEMICAL NAME, ,MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

CHEMICAL NAME: alpha 1,4 polyglucopyranose

MOLECULAR FORMULA $[C_6H_{10}O_5]_n$

MOLECULAR WEIGHT 13,000 – 19,000 Dalton

STRUCTURAL FORMULA



17. RELATED/SUPPORTING DOCUMENTS:

IND [redacted] Extraneal (7.5% icodextrin solution)
NDA 17-512 Dianeal, Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 Dianeal, Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 Dianeal. Low calcium in Ultrabag Container

DMF List (From Review # 1 and 2)

DMF #	Subject	Holder	Status	Review Date	LOA date
[redacted]	Icodextrin	[redacted]	ADEQUATE	09-26-01	11-15-00
[redacted]	Polyvinyl Chloride Plastic	Baxter Healthcare Corporation	ADEQUATE	10-04-99	N/A

18. STATUS:

As per previous reviews, the status of all disciplines except Office of Compliance was ACCEPTABLE. The Office of Compliance (OC) updated a July 16, 2001 WITHHOLD overall recommendation to ACCEPTABLE on September 10, 2002.

The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As noted in CMC review # 2, there were no other CMC deficiencies except a WITHHOLD from the Office of Compliance . The status of overall recommendation was updated to ACCEPTABLE on September 10, 2002. The NDA may be approved from the Chemistry Manufacturing and Controls standpoint. A copy of the EER is attached at the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug product Extraneal (7.5% icodextrin) is — sterilized, nonpyrogenic, clear peritoneal dialysis solution available in Ultra Bag and Ambu-Flex containers with fill volumes of 1.5 L, 2.0 L, and 2.5 L. Each 100 mL of Extraneal contains 7.5 grams of icodextrin in an electrolyte solution with 40 mEq/L lactate.

The drug substance Icodextrin is a white amorphous powder, — — of 10% w/v aqueous solution. Icodextrin is starch derived, large molecular weight, water soluble glucose polymer linked by alpha (1-4) and less than 10% alpha (1-6) glucosidic bonds. Icodextrin has a Weight Average Molecular Weight between 13,000 - 19,000 Daltons and Number Average Molecular Weight between 5,000 – 6,500 Daltons. Icodextrin is isolated by fractionation of maltodextrin. Maltodextrin is obtained by the partial hydrolysis of corn starch, and is affirmed as generally regarded as safe (GRAS) in 21 CFR 184.1444 as a food ingredient.

ML Laboratories is the manufacture of drug substance icodextrin.

The incidences of cloudy effluent were identified in non-US Extraneal product, manufactured from icodextrin produced by — Investigation indicated that presence of — ng/mL, may be associated with an increase in post market safety reports for cloudy effluent/sterile peritonitis. The applicant initiated a recall of Extraneal manufactured from icodextrin produced by . —

Although, Extraneal manufactured from supplier of icodextrin for this NDA did not contain detectable levels of [redacted] as a precautionary measure, the Agency recommended that a [redacted] limit of [redacted] ng/mL be included in the specifications of Extraneal.

Method Validation by Agency will be initiated shortly.

The proposed indication for Extraneal is for long dwell exchange in peritoneal dialysis, for treatment of chronic renal failure. Extraneal is an isosmotic peritoneal dialysis solution containing glucose polymers (icodextrin) as the primary osmotic agent. Icodextrin functions a colloid osmotic agent to achieve sustained ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in a steady rate of trans-capillary ultrafiltration throughout the dwell. Extraneal also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.

B. Description of How the Drug Product is Intended to be Used

Extraneal is intended for intraperitoneal administration only. It should be administered only as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. The recommended dwell time is 8 to 16 hours.

Extraneal should be administered over a period of 10 - 20 minutes at a rate that is comfortable for the patients. Aseptic technique should be used throughout the peritoneal dialysis procedure. To reduce possible discomfort during administration, solution may slightly be warmed prior to use.

Based on long-term stability data and 6-month accelerated data an expiration date of 18 month is recommended. Extraneal is stored at 20-25° C (68°-77° F). Excursions permitted to 15-30° C (59°-86° F).

C. Basis for Approvability or Not-Approval Recommendation

N/A.

III. Administrative

A. Reviewer's Signature
B. Endorsement Block
C. CC Block

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/s/

Ramsharan Mittal
12/12/02 11:14:00 AM
CHEMIST

Kasturi Srinivasachar
12/12/02 12:17:09 PM
CHEMIST

CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-321 **DATE REVIEWED:** September 26, 2001

REVIEW #: 2 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N-BZ Amendment	19-SEP-01	20-SEP-01	

NAME & ADDRESS OF SPONSOR: Baxter Health care Corporation
1620 Waukegan Road
McGaw Park, IL 60885

DRUG PRODUCT NAME
Proprietary: EXTRANEAL
Established: Icodextrin
Code Name/#: Dextrin 20 and Polyglucose
Chem.Type/Ther.Class: 1

PHARMACOL. CATEGORY/INDICATION: Treatment of Chronic Renal Failure
DOSAGE FORM: LVP Peritoneal Dialysis Solution
STRENGTHS: 7.5%w/v
ROUTE OF ADMINISTRATION: Intraperitoneal

Rx/OTC: __x__ Rx _____ OTC

SPECIAL PRODUCTS: _____ Yes __x__ No

(If yes, fill out the form for special products and deliver to TIA through Team leader for data entry)

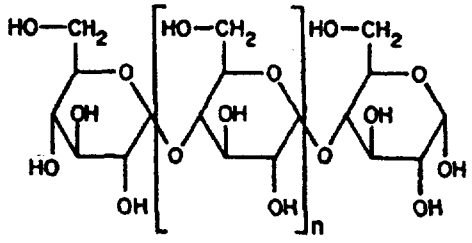
CHEMICAL NAME: alpha 1,4 polyglucopyranose

CAS REGISTRY NO. 9004-53-9

MOLECULAR FORMULA $[C_6H_{10}O_5]_n$

MOLECULAR WEIGHT

STRUCTURAL FORMULA



RELATED DOCUMENTS:

IND [redacted] Extraneal (7.5% icodextrin solution)
NDA 17-512 (Dianeal Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 (Dianeal Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 (Dianeal Low calcium in Ultrabag Container

Table I. DMF List (Vol. 2, Pages 10-11, 84)

DMF #	Subject	Holder	Status	Review Date	LOA date
[redacted]	Icodextrin	—	ADEQUATE	09-26-01	11-15-00
[redacted]	Polyvinyl Chloride Plastic	Baxter Healthcare Corporation	ADEQUATE	10-04-99	N/A

CONSULTS:

As noted in Review # 1, EER Status of one of the facilities is still WITHHOLD.

OPDRA has approved the product name Extraneal.

Microbiology review has been completed with recommendation for approval.

USAN is still in the process of evaluating icodextrin name and its proposed chemical structure.

REMARKS/COMMENTS:

DMF # [redacted] was INADEQUATE in Review # 1 and has been amended (August 31, 2001) with satisfactory responses to all deficiencies. This DMF is now ADEQUATE (DMF review # 2, September 26, 2001).

Method Validation by Agency will be initiated at a later date.

Deficiencies of NDA Review # 1 (September 7, 2001) sent to the applicant have been satisfactorily addressed and are the subject of this review.

CONCLUSIONS & RECOMMENDATIONS:

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 enquire 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.

/S/

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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/s/

Ramsharan Mittal
9/26/01 05:51:42 PM
CHEMIST

Kasturi Srinivasachar
9/26/01 06:25:56 PM
CHEMIST

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-321 **DATE REVIEWED:** September 7, 2001

REVIEW #: 1 **REVIEWER:** Ramsharan D. Mittal

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	20-DEC-00	27-DEC-00	28-DEC-00
N-BZ	20-MAR-01	22-MAR-01	
N-BZ	16-MAY-01	18-MAY-01	
N-BZ	23-MAY-01	25-MAY-01	
BL	13-JUN-01	14-JUN-01	

NAME & ADDRESS OF SPONSOR: Baxter Health care Corporation
1620 Waukegan Road
McGaw Park, IL 60885

DRUG PRODUCT NAME
Proprietary: EXTRANEAL
Established: Icodextrin
Code Name/#: Dextrin 20 and Polyglucose
Chem.Type/Ther.Class: 1

PHARMACOL. CATEGORY/INDICATION: Treatment of Chronic Renal Failure
DOSAGE FORM: LVP Peritoneal Dialysis Solution
STRENGTHS: 7.5%w/v
ROUTE OF ADMINISTRATION: Intraperitoneal

Rx/OTC: _x_ Rx _____ OTC

SPECIAL PRODUCTS: _____ Yes _x_ No

(If yes, fill out the form for special products and deliver to TIA through Team leader for data entry)

CHEMICAL NAME: alpha 1,4 polyglucopyranose

CAS REGISTRY NO. 9004-53-9

MOLECULAR FORMULA $[C_6H_{10}O_5]_n$

MOLECULAR WEIGHT

STRUCTURAL FORMULA

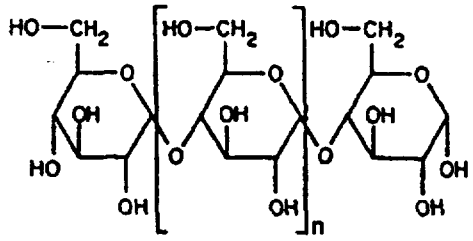

Table I. DMF List (Vol. 2, Pages 10-11, 84)

DMF #	Subject	Holder	Status	Review Date	LOA date
[redacted]	Icodextrin	[redacted]	IN-ADEQUATE	07-15-01	11-15-00
[redacted]	Polyvinyl Chloride Plastic	Baxter Healthcare Corporation	ADEQUATE	10-04-99	N/A

RELATED DOCUMENTS:

IND [redacted] Extraneal (7.5% icodextrin solution)
NDA 17-512 (Dianeal Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 (Dianeal Peritoneal Dialysis Solution in Plastic Container
NDA 20-163 (Dianeal Low calcium in Ultrabag Container

CONSULTS:

There were some concerns about the starting material for the manufacture of icodextrin in DMF [redacted] To resolve the issue. a teleconference was arranged between the Agency, ML Laboratories and Baxter. The response was further discussed with Dr. Yuan-Yuan Chiu, Director ONDC and Dr. Duu Gong Wu, Team leader DNDCII. Details of the teleconference and consultation are provided in the DMF review.

OPDRA has approved the product name Extraneal.

Microbiology review has been completed with recommendation for approval.

EER Status of one of the facilities is WITHHOLD. A copy of the EER is attached at the end of this review.

USAN is still in the process of evaluating icodextrin name and its proposed chemical structure.

REMARKS/COMMENTS:

Extraneal Peritoneal Dialysis is a sterile, aqueous solution with electrolytes and lactate and containing 7.5% icodextrin as the primary osmotic agent. The electrolyte composition and buffer(lactate) are identical to the PD-2 formulation of Dianeal PD-2, an approved solution for PD use in the USA (NDA 17-512) which contains glucose as the primary osmotic agent.

DMF # [redacted] is IN-ADEQUATE. DMF holder is being notified to resolve few issues and also update their DMF with the information they sent by e-mail. This information is included in the DMF review. The DMF concerns are not very serious and are expected to be resolved soon.

Method Validation by Agency will be initiated at a later date.

CONCLUSIONS & RECOMMENDATIONS:

The DMF # [redacted] remains to be updated. EER status of one facility is WITHHOLD. The Office of Compliance has issued a WITHHOLD overall recommendation. Based on various deficiencies as noted in the section H and the EER status the application is NOT APPROVABLE until the applicant satisfactorily addresses these.

/S/

Ramsharan D. Mittal Ph.D.,
Review Chemist

/S/

Kasturi Srinivasachar, Ph.D.,
Chemistry, Team Leader

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21321/000**
Priority: **1S** Org Code: **110**
Stamp: **22-DEC-2000** Regulatory Due: **22-OCT-2001** Action Goal: District Goal: **23-AUG-2001**
Applicant: **BAXTER HLTHCARE**
940 WOODLANDS PKY
VERNON HILLS, IL 60061
Brand Name: **EXTRANEAL(ICODEXTRIN)7.5%W/V PD SOLUTION**
Established Name:
Generic Name: **ICODEXTRIN**
Dosage Form: **INJ (INJECTION)**
Strength: **7.5% W/V**

FDA Contacts: **ID = 127376** , **Project Manager**
R. MITTAL (HFD-110) **301-594-5353** , **Review Chemist**
K. SRINIVASACHAR (HFD-110) **301-594-5376** , **Team Leader**

Overall Recommendation:

WITHHOLD on 09-NOV-2001 by B. HARTMAN (HFD-324) 301-827-0067
WITHHOLD on 16-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1025114**
BAXTER HEALTHCARE CORP
HWY 221 NORTH NORTH COVE
MARION, NC 28752
DMF No:
AADA No:

Profile: **LVP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Establishment: **1416980**
BAXTER HEALTHCARE CORP
REGULATORY AFFAIRS
RT 120 AND WILSON RD
ROUND LAKE, IL 60073
DMF No:
AADA No:

Profile: **CTL** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-NOV-2001**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER

Establishment: **9617711**
ML LABORATORIES PLC
104A WEST STREET
FARNHAM, SURREY, UK GU9 7EN
DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **12-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21321/000**
Priority: **1S** Org Code: **110**
Stamp: **22-DEC-2000** Regulatory Due: **22-OCT-2001** Action Goal: District Goal: **23-AUG-2001**
Applicant: **BAXTER HLTHCARE**
940 WOODLANDS PKY
VERNON HILLS, IL 60061
Brand Name: **EXTRANEAL(ICODEXTRIN)7.5%W/V PD SOLUTION**
Established Name:
Generic Name: **ICODEXTRIN**
Dosage Form: **INJ (INJECTION)**
Strength: **7.5% W/V**

FDA Contacts:
J. GUZMAN (HFD-110) 301-594-5300 , Project Manager
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

WITHHOLD on 16-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1025114**
BAXTER HEALTHCARE CORP
HWY 221 NORTH
MARION, NC 28752
DMF No:
AADA No:

Profile: **LVP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Establishment: **1416980**
BAXTER HEALTHCARE CORP
REGULATORY AFFAIRS
RT 120 AND WILSON RD
ROUND LAKE, IL 60073
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JUN-2001**
Decision: **WITHHOLD**
Reason: **EIR REV-NONCONCUR W/DISTRIC**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER

Establishment: **9617711**
ML LABORATORIES PLC
104A WEST STREET
FARNHAM, SURREY, UK GU9 7EN
DMF No:
AADA No:

Profile: **CRU** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-JUL-2001**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21321/000
Stamp: 22-DEC-2000
Regulatory Due: 22-OCT-2001
Applicant: BAXTER HLTHCARE
940 WOODLANDS PKY
VERNON HILLS, IL 60061
Priority: 1S
Org Code: 110

Action Goal:
District Goal: 23-AUG-2001
Brand Name: EXTRANEAL(ICODEXTRIN)7.5%W/V PD SOLUTION
Estab. Name:
Generic Name: ICODEXTRIN

Dosage Form: (INJECTION)
Strength: 7.5% W/V

Application Comment: ML LABORATORIES
IS THE FACILITY FOR MANUFACTURE OF DRUG SUBSTANCE
THERE IS NO CFN NUMBER FOR THIS FACILITY. PLEASE ADD THIS TO THE LIST OF FACILITIES TO BE INSPECTED.

2-27-01: THE DRUG SUBSTANCE ICODEXTRINE IS MANUFACTURED BY

THE PROFILE CLASS "CRU" WAS USED TO CLASSIFY THE DRUG SUBSTANCE AS THERE IS NONE WHICH FITS THE MANUFACTURING PROCESS OF THIS DRUG SUBSTANCE.

CHEMIST IS LIKELY TO ACCOMPANY THE INVESTIGATOR FOR THE INSPECTION OF THE DRUG SUBSTANCE MANUFACTURING FACILITY, ML LABORATORIES.

DOSAGE FORM: THE DRUG PRODUCT EXTRANEAL IS (7.5% ICODEXTRIN) PERITONEAL DIALYSIS SOLUTION. THERE IS NO DOSAGE FORM WHICH DESCRIBES THIS DOSAGE FORM. THIS DOSAGE FORM IS SIMILAR TO PARENTERAL DRUG PRODUCTS AND INJECTION IS THE CLOSEST WHICH WAS USED. BUT A NEW DOSAGE FORM SHOULD BE ASSIGNED TO THIS PRODUCT. (on 27-FEB-2001 by R. MITTAL (HFD-110) 301-594-5353)

FDA Contacts: J. GUZMAN (HFD-110) 301-594-5300 , Project Manager
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation: WITHHOLD on 16-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1025114
BAXTER HEALTHCARE CORP
HWY 221 NORTH
MARION, NC 28752

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: LVP OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				MITTALR
SUBMITTED TO DO	09-FEB-2001	PS			FERGUSONS
ASSIGNED INSPECTION	09-FEB-2001	PS			LANDREWS
INSPECTION PERFORMED	01-MAY-2001		27-APR-2001		VSTOAKES
INVESTIGATOR NOTED PROFILE CLASS SHOULD BE "LVP". GMP STATUS WAS ACCEPTABLE.					
DO RECOMMENDATION	01-MAY-2001			ACCEPTABLE INSPECTION	VSTOAKES
INSPECTION PERFORMED 4/24/2001 WAS CLASSIFIED NAI. INVESTIGATOR NOTED PROFILE CLASS SHOULD BE "LVP". THIS PROFILE WAS ACCEPTABLE.					
FINAL PROCESS VALIDA	01-MAY-2001			APPROVE	VSTOAKES
FINAL VALIDATION ACCEPTABLE BASED UPON 4/24/2001 INSPECTION.					

OC RECOMMENDATION 10-JUL-2001 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment: 1416980
BAXTER HEALTHCARE CORP
RT 120 AND WILSON RD
ROUND LAKE, IL 60073
DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				MITTALR
SUBMITTED TO DO	09-FEB-2001	GMP			FERGUSONS
ASSIGNED INSPECTION	26-FEB-2001	PS			LJARRELL
INSPECTION SCHEDULED	05-JUN-2001		18-MAY-2001		LJARRELL
INSPECTION PERFORMED	05-JUN-2001		18-MAY-2001		LJARRELL
LACK OF A STABILITY INDICATING METHOD FOR ROUTINE STABILITY TESTING OF ICODEXTRIN WAS THE MOST SIGNIFICANT ITEM NOTED. FIRM PROMISED TO CONTINUE THE TEST WHICH WAS DONE ON LOTS.					
DO RECOMMENDATION	19-JUN-2001			ACCEPTABLE ADEQUATE FIRM RESPONSE	LJARRELL
FIRM COMMITTED TO CONTINUE THE STABILITY INDICATING TEST FOR ICODEXTRIN POST APPROVAL RATHER THAN DISCONTINUING IT AS PROPOSED.					
OC RECOMMENDATION	20-JUN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
EIR RECEIVED BY OC	21-JUN-2001				HARTMANB
OC RECOMMENDATION	26-JUN-2001			WITHHOLD EIR REV-NONCONCUR W/DISTRICT	HARTMANB
DO RECOMMENDED ACCEPTABLE, EIR REVIEW FOUND POTENTIALLY SERIOUS PROBLEMS, OC RECOMMENDATION WITHHOLD					

Establishment: 9617711
ML LABORATORIES PLC
104A WEST STREET
FARNHAM, SURREY, UK GU9 7EN
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CRU OAI Status: POTENTIAL OAI
Estab. Comment: REVIEW CHEMIST WOULD LIKE TO ACCOMPANY INVESTIGATOR ON INSPECTION. (on 27-FEB-2001 by S. FERGUSON (HFD-324) 301-827-0062)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-FEB-2001				MITTALR
SUBMITTED TO DO	27-FEB-2001	GMP			EGASM
ASSIGNED INSPECTION	27-FEB-2001	GMP			EGASM
INSPECTION SCHEDULED	03-MAY-2001		31-MAY-2001		IRIVERA
INSPECTION PERFORMED	01-JUN-2001		31-MAY-2001		EGASM
EIR RECEIVED BY OC	27-JUN-2001				FERGUSONS
OC RECOMMENDATION	12-JUL-2001			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

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

/s/

Ramsharan Mittal
9/10/01 01:00:20 PM
CHEMIST

Kasturi Srinivasachar
9/10/01 01:47:43 PM
CHEMIST

Methods Validation

Methods Validation by the Agency will be requested at a later date (see Dr. Mittal's 9-10-01 and 9-26-01 reviews).

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commercial

information

3.6 Environmental Assessment

REQUEST FOR CATEGORICAL EXCLUSION

Pursuant to Title 21 CFR 25.31(c), Baxter Healthcare Renal Division requests a categorical exclusion from the requirement for the preparation of an Environmental Assessment for Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution, a drug that is being investigated for long dwell exchanges in peritoneal dialysis. Under 21 CFR25.31(c), action on an NDA is categorically excluded from the preparation of an Environmental Assessment for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment.

Active Pharmaceutical Ingredient and Physical/Chemical Characteristics
The active pharmaceutical ingredient is icodextrin, a large molecular weight, water soluble glucose polymer. Icodextrin is isolated by fractionation of maltodextrin. Maltodextrin is obtained by the partial hydrolysis of cornstarch, and is affirmed as generally regarded as safe (GRAS) in 21 CFR 184.1444 as a food ingredient. A summary of available physical/chemical characteristics of the active pharmaceutical ingredient is given below.

Generic Name
Icodextrin

Chemical Name
α 1,4 – polyglucopyranose

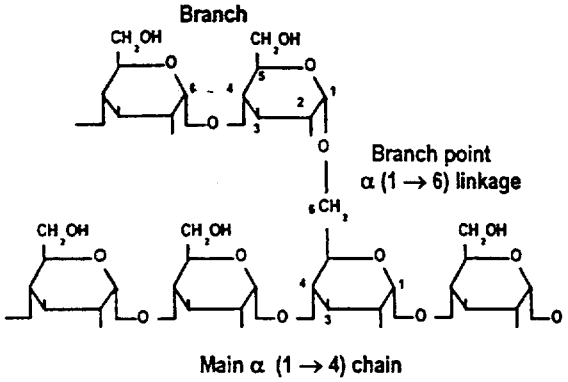
CAS Number
9050-36-6

Molecular Formula
$[C_6H_{10}O_5]_n$

Molecular Weight
85% of molecules have molecular weights of between —
Weight Average MW = 5,000-6,500

Numerical Average Molecular Weight Mn = —

Structural Formula



Water solubility
Freely Soluble in Water,
(Specification is no less than 200grams/Liter at 25C)

pH

% w/v aqueous solution

Other components of the product are electrolytes, contained in the following concentrations:

sodium chloride	5.4 g/l
magnesium chloride	0.051 g/l
calcium chloride	0.257 g/l
sodium lactate	5.5 g/l

These are salts that are already currently used in existing peritoneal dialysis formulations.

Rationale for Categorical Exclusion under 21 CFR 25.31(c)

Peritoneal dialysis is the technique of using the body's peritoneal membrane as a natural filter to remove waste and water via placement of a catheter into the abdominal cavity and repeated installation and drainage of sterile dialysis solution. The dialysate consists of an aqueous solution of electrolytes to maintain normal electrolyte balance, a source of alkali to maintain acid-base status, and an osmotic agent to facilitate removal of water.

For Extraneal™, icodextrin is the osmotic agent. The intent is to replace, in part or whole, the currently marketed peritoneal dialysis solutions, which use dextrose with Extraneal™ as the polysaccharide osmotic agent. Patients on peritoneal dialysis will perform multiple exchanges each day. Extraneal™ is intended to replace one of the patient's dextrose exchanges.

- A portion (~ 40%) of the icodextrin in the dialysis solution is absorbed into the patient's circulation where it is metabolized to smaller glucose polymers, such as maltose. As shown in several metabolism studies in both laboratory animals and humans, icodextrin, like other naturally occurring carbohydrates, is metabolized in the body by enzymes such as amylase and maltase, into maltose and to a much lesser extent, glucose and maltotriose.

The drug product and its metabolites will primarily be excreted into the sanitary sewer system in the patient's home, with ultimate breakdown in the public water treatment system.

As previously described, icodextrin is isolated by fractionation of naturally occurring materials, in this case, cornstarch, and therefore behaves as a naturally occurring polysaccharide in biological systems. Both toxicology studies and metabolism studies have shown a lack of toxicity and breakdown to naturally occurring sugars, respectively. Icodextrin has been evaluated in toxicity tests in animals (rats, mice, dogs,) for a duration of up to 28 days and has demonstrated to have a very low order of toxicity in these studies. Icodextrin was negative for mutagenic potential when evaluated in studies for assessing gene mutation and chromosomal effects, including an Ames Salmonella gene mutation assay, chromosomal aberration in CHO cells and an in vivo mouse micronucleus test. Clinical studies have shown a benefit of the use of Extraneal™ as compared to dextrose in the current application.

The use of Extraneal™ product will not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment as it is intended to replace an existing polysaccharide with another polysaccharide which breaks down into the same sugar-based moieties as what is currently used. Extraneal™ is made of naturally occurring materials including an extract of cornstarch, and salts, components that are considered GRAS as food additives. Furthermore, it has been reported that dextrins, including starch and maltose, are preferred substrates as compared to glucose for activated sludge bacteria in municipal wastewater treatment systems [Ubukata, Y. and S. Takii (1998). Effect of acclimating saccharides on the activated sludge bacterial population: composition abnormality of activated sludge acclimated to glucose. Water Science and Technology 37:99-103].

The total amount of units (i.e., packages) of peritoneal dialysis solution in use in the United States is not expected to increase due to icodextrin/Extraneal™ product being marketed. Extraneal™ is intended as a substitute for an existing approved marketed dialysis product. The total amount of all plastic packaging components will also not increase. Returned good and disposal of product from patient home use and from dialysis center will be disposed on in the same manner as existing approved dialysis units.

Summary

Baxter Healthcare Renal Division hereby states that the proposed NDA for Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution complies with the requirements of 21

CFR25.31(c), and that no extraordinary circumstances exist under 21 CFR25.21. The product is naturally occurring; its metabolites will be similar to those generated by currently approved products and there will be no significant change in the amount of waste in the environment from use of this product.