

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Approval Letter(s)



NDA 21-321

Baxter Healthcare Corporation
Attention: Dr. Lisa Skeens
1620 Waukegan Road
McGaw Park, IL 60085

Dear Dr. Skeens:

Please refer to your new drug application (NDA) dated December 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution.

We acknowledge receipt of your submissions dated October 30, November 6, 19, 27 and December 12, 17, 26, 2001; January 23, February 28, March 21, April 4, 18, 25, May 14, 22, June 28, July 11, 30, 31, August 29, September 11, 17, 25, October 1, 2, 15, 21, 28 and November 4, 6, 2002. The November 6, 2002 submission constituted a complete response to our October 22, 2001 approvable letter.

This new drug application provides for the use of Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution 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.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted final printed labeling (package insert and patient package insert included in your submission of November 6, 2002). Accordingly, the application is approved effective on the date of this letter.

At the time of your next printing, please make the following editorial changes to the labeling:

1. Under **Clinical Studies/Ultrafiltration, Urea and Creatinine Clearance**, the first sentence in the first paragraph should be changed from:

In the active-controlled trials of one to six months in duration described below, EXTRANEAL used once-daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration compared with 1.5% and 2.5% dextrose solutions, and higher creatinine and urea nitrogen clearances when compared to 2.5% dextrose.

To:

In the active-controlled trials of one to six months in duration, described below, EXTRANEAL used once-daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration than 1.5% and 2.5% dextrose solutions, and higher creatinine and urea nitrogen clearances than 2.5% dextrose.

2. Under **Clinical Studies/Ultrafiltration, Urea and Creatinine Clearance**, the text appearing under Figures 1 and 2 should be changed from:

...mean change from baseline

To:

...Extraneal vs. 2.5% dextrose

3. Under **Clinical Studies/Ultrafiltration, Urea and Creatinine Clearance**, the first sentence in the second paragraph should be changed from:

In 175 CAPD patients randomized to EXTRANEAL (N=90) or 2.5% dextrose solution (N=85) for the 8-15 hour overnight dwell for one month, mean net ultrafiltration for the overnight dwell was significantly greater for the EXTRANEAL group compared to the 2.5% dextrose group when evaluated at weeks 2 and 4 (Figure 1).

To:

In 175 CAPD patients randomized to EXTRANEAL (N=90) or 2.5% dextrose solution (N=85) for the 8-15 hour overnight dwell for one month, mean net ultrafiltration for the overnight dwell was significantly greater in the EXTRANEAL group at weeks 2 and 4 (Figure 1).

4. Under **Clinical Studies/Ultrafiltration, Urea and Creatinine Clearance**, the last sentence in the third paragraph should be changed from:

Mean creatinine and urea nitrogen clearances were significantly greater for EXTRANEAL compared with 2.5% dextrose at weeks 6 and 12 ($p < 0.001$).

To:

Mean creatinine and urea nitrogen clearances were significantly greater for EXTRANEAL than 2.5% dextrose at weeks 6 and 12 ($p < 0.001$).

5. Under **Clinical Studies/Ultrafiltration, Urea and Creatinine Clearance**, the last sentence in the fourth paragraph should be changed from:

The ultrafiltration results were not significantly different.

To:

There was no significant difference between the two groups with respect to ultrafiltration.

6. Under **WARNINGS**, the first sentence in the second paragraph should be changed from:

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

To:

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

7. Under **PRECAUTIONS/Information for Patients**, the first sentence should be changed from:

Patients should be instructed not to use solutions if they are cloudy, discolored, contain visible particulate matter, or if they have evidence of leaking containers.

To:

Patients should be instructed not to use solutions if they are cloudy, discolored, contain visible particulate matter, or if they show evidence of leaking containers.

8. Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the first sentence in the second paragraph should be changed from:

A fertility study in rats where males and females were treated for four and two weeks, respectively, prior to mating and until day 17 of gestation at up to 1/3 the human exposure on a mg/m² basis revealed slightly low epididymal weights in parental males in the high dose group (1.5mg/kg/day) as compared to Control.

To:

A fertility study in rats where males and females were treated for four and two weeks, respectively, prior to mating and until day 17 of gestation at up to 1.5mg/kg/day (1/3 the human exposure on a mg/m² basis) revealed slightly low epididymal weights in parental males in the high dose group as compared to Control.

9. Under **ADVERSE REACTIONS**, the first sub-heading (**Adverse Reactions from Clinical Trials-Significance of Adverse Reaction Data Obtained from Clinical Trials**) should be removed.

10. Under **ADVERSE REACTIONS**, in the second paragraph, a comma should be added after the word "Hispanic."

11. Under **ADVERSE REACTIONS**, the paragraph which precedes Table 1 should be changed from:

A listing of adverse events reported in these same clinical studies, regardless of causality, occurring in $\geq 5\%$ of patients and more common on EXTRANEAL is presented in Table 1.

To:

Table 1 shows the adverse events reported in these clinical studies, regardless of causality, occurring in $\geq 5\%$ of patients and more common on EXTRANEAL than control.

12. Under **ADVERSE REACTIONS**, the eighth paragraph should be added to the end of the seventh paragraph, and should be changed from:

All reported events are included except those already listed in Table 1, those not plausibly associated with EXTRANEAL, and those that were associated with the condition being treated or related to the dialysis procedure.

To:

All reported events are included in the list except those already listed in Table 1 or the following two paragraphs, those not plausibly associated with EXTRANEAL, and those that were associated with the condition being treated or related to the dialysis procedure.

13. Under **ADVERSE REACTIONS/Peritoneal Dialysis-Related**, the first sentence should be changed from:

Adverse events common to the treatment modality of peritoneal dialysis including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain were observed at a similar frequency with EXTRANEAL and Controls (See **PRECAUTIONS**).

To:

Adverse events common to the peritoneal dialysis, including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain, were observed at a similar frequency with EXTRANEAL and Controls (See PRECAUTIONS).

14. Under **ADVERSE REACTIONS/Changes in Alkaline Phosphatase and Serum Electrolytes**, the second sentence in the first paragraph should be changed from:

No associated increases in liver function tests were observed.

To:

No associated increases in other liver chemistry tests were observed.

15. Under **ADVERSE REACTIONS/Changes in Alkaline Phosphatase and Serum Electrolytes**, the last sentence in the second paragraph should be changed from:

Although these decreases have been small and clinically unimportant, monitoring of the patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

To:

Although these decreases have been small and clinically unimportant, monitoring of patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

16. Under **OVERDOSAGE**, the second and third sentences should be changed from:

Overdosage of EXTRANEAL may result in higher levels of serum icodextrin and metabolites. It is unknown what symptoms may be caused from exposure in excess of those observed in clinical trials.

To:

Overdosage of EXTRANEAL would be expected to result in higher levels of serum icodextrin and metabolites, but it is not known what signs or symptoms might be caused by exposure in excess of the exposures used in clinical trials.

17. Under **DOSAGE AND ADMINISTRATION**, the sixth paragraph should be changed from:

Do not use if the product is cloudy or discolored, if it contains particulate matter, or if the container is leaky.

To:

Do not use Extraneal if it is cloudy or discolored, if it contains particulate matter, or if the container is leaky.

We remind you of your postmarketing study commitments related to the potential for erroneous measurement of serum glucose in patients using Extraneal, agreed to in a teleconference with the Division on November 5, 2002. These commitments are listed below.

1. To develop and carry-out a survey to assess the ability of both patients and health care professionals to obtain prompt, accurate information regarding the method of glucose measurement used for a given test strip and monitor. This survey should be carried out in a representative sample of patients starting Extraneal during the first year following approval and the results of this survey should be

- analyzed and included in the first Annual Report. Sample survey forms, a description of the methodology (including sample size), and a proposed benchmark of success should be submitted to the FDA for review prior to starting the survey.
2. To initiate an ongoing discussion with the manufacturers of the various glucose strips and monitors to ensure their awareness of the need to provide adequate information for patients who contact them regarding the specific enzyme system used by their respective test strips. A summary of all activities related to this program should be included in each Annual Report.
 3. To develop and carry-out an education program for providers of emergency health care (*i.e.*, ambulance and emergency room personnel) and other healthcare staff caring for these patients chronically (*e.g.*, dialysis nurses and nephrologists) to inform them of the potential for inaccurate measurement of serum glucose levels when patients are receiving Extraneal and to provide them sources of information about individual test strip and monitors. A summary of all activities related to this program should be included in each Annual Report.
 4. To report all events related to hypoglycemia in patients receiving Extraneal to the FDA as 15-day reports, regardless of their perceived relationship to drug. These reports should also be summarized in a special section of the Annual Report.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardio-Renal Drug Products, and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-321

Approvable Letter (S)



NDA 21-321

Baxter Healthcare Corporation
Attention: Ms. Mary Kay Rybicki
1620 Waukegan Road
McGaw Park, IL 60085

Dear Ms. Rybicki:

Please refer to your new drug application (NDA) dated December 22, 2000, received December 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution.

We acknowledge receipt of your submissions dated January 29, March 20, April 5, 11, 16, and 18, May 3, 16, and 23, June 13, July 17 and 30, August 29, 30, and 31, and September 19, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

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

/s/

Robert Temple
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28 pages redacted from this section of
the approval package consisted of draft labeling