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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

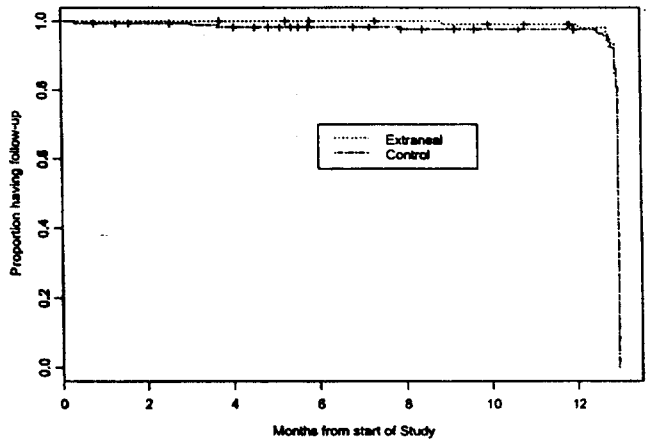
21-321

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION AMENDMENT

NDA #:	21-321
Related IND #:	—
Applicant:	Baxter Healthcare Corporation
Name of Drug:	Extraneal™ (Icodextrin)
Indication:	Treatment of chronic renal failure
Document reviewed:	Electronic data
Date of submission:	August 1, 2001
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Stephen Fredd, M.D. (HFD–110)

According to the sponsor, the previous data from Study RD-97-CA-131 that was submitted for review did not contain the complete survival data for all patients. Specifically, if a patient completed the 12-month study, the original data set recorded 365 days of survival for this patient even if the patient was known to be alive 13 months after randomization. In this case, the number of days of survival should be 395 days. This affected a large number of patients, but the effect on the analysis was very minor. The purpose of this amendment is to simply confirm that the survival status at month 13 was known for most patients. 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%. The following graph should be used in place of Figure A1 in the review to represent the estimated probabilities of having known survival status.



/S/

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 2 pages of text and figures.

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LAWRENCEJ/594–5375/amendment.doc/08/01/01

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8/10/01 03:58:48 PM
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STATISTICAL REVIEW AND EVALUATION

NDA #:	21-321
Related IND #:	—
Applicant:	Baxter Healthcare Corporation
Name of Drug:	Extraneal™ (Icodextrin)
Indication:	Treatment of chronic renal failure
Document reviewed:	Volume 1-155
Date of submission:	December 22, 2000
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Stephen Fredd, M.D. (HFD–110)

1. Introduction

On October 19, 2000, a closed session of the Cardio-Renal Advisory Committee was held and the 12-month safety study RD-97-CA-131 was discussed. The protocol had required only 30-day follow-up for patients who had withdrawn from the study. The committee asked to see the results of the mortality analysis for the 12-month intended duration of treatment and for 30 days thereafter. The document under review here relates to this analysis in the addendum to the clinical report for this study.

2. Study Design

Study RD-97-CA-131 was a 52-week prospective, double-blind, randomized, active-controlled, parallel group study comparing the safety of Extraneal with dextrose for the long dwell in Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD) patients. 287 patients (112 control and 175 Extraneal) were enrolled in the study.

3. Planned Statistical Analysis

The original analysis of mortality required 30-day follow-up for patients who had withdrawn or completed the study. Based on the comments from the Advisory Committee, patients' status for the intended 12-month duration of the study plus 30 days thereafter was analyzed.

4. Results

The mortality status of 17 patients was not known after 360 days from the start of the study (6 control and 11 Extraneal). The status of 161 patients was not known 375 days from the start of the study (59 control and 102 Extraneal). The status of 168 patients was not known 395 days from the start of the study (63 control and 105 Extraneal). The

Kaplan-Meier estimates of the probability of having follow-up at each time point for each group appears in the appendix.

Using the mortality data for the 12-month intended treatment period plus 1 month additional follow-up, a total of 29 patients died. This includes 20 patients from the Extraneal group (20/175 = 11.4%) and 9 patients from the control group (9/118 = 8.0%). The Kaplan-Meier estimates of the survival curves appear in Figure 4.1.

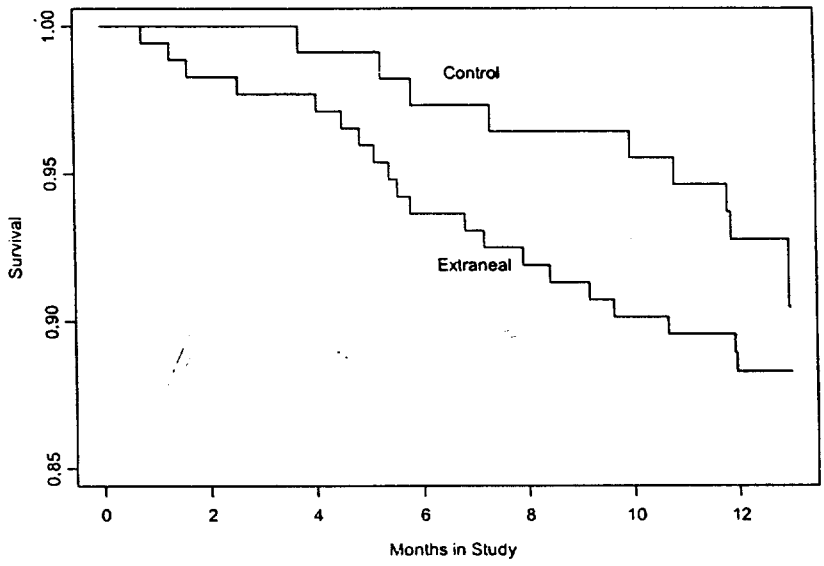

Figure 4.1 Kaplan-Meier estimates of survival curves using available data with 13-months of follow-up.

The value of the logrank statistic is not significant (p=0.305). However, insufficient evidence to rule out equality of the two curves is not the same thing as proving that there is no difference in the 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). This estimate is from a Cox regression model with one term for treatment group. In order to subjectively evaluate the two survival curves, the Medical Officer wanted to examine the 80% confidence intervals for mortality rates at each month. The choice of 80% was pre-specified according to the Medical Officer. The point estimates and lower and upper bounds of the 80% confidence intervals for each group are in Table 4.1.

Table 4.1 Point estimates and 80% confidence interval for survival in each group.

Month	Extraneal			Control		
	Lower bound	Point estimate	Upper bound	Lower bound	Point estimate	Upper bound
1	0.987	0.994	1.000		1.000	
2	0.970	0.983	0.995		1.000	
3	0.963	0.977	0.992		1.000	
4	0.963	0.977	0.992	0.980	0.991	1.000
5	0.941	0.960	0.979	0.980	0.991	1.000
6	0.913	0.936	0.960	0.954	0.973	0.993
7	0.906	0.930	0.956	0.954	0.973	0.993
8	0.893	0.919	0.946	0.942	0.964	0.987
9	0.886	0.913	0.941	0.942	0.964	0.987
10	0.873	0.901	0.931	0.931	0.955	0.981
11	0.866	0.896	0.926	0.919	0.946	0.974
12	0.852	0.883	0.915	0.896	0.928	0.960

The 80% confidence intervals overlap except at months 5 and 9 where the upper limit of the confidence interval for the Extraneal group is 0.001 below the lower limit for the control group. The standard error (and consequently, the confidence limits) could not be estimated for the first three months in the control group because all patients survived at least 3 months in that group.

The amendment to the study report states that exploratory analyses (Cox regression models) were done to determine whether any baseline characteristics could explain the numerical difference in mortality between the two groups. The covariates that were studied included: age, race, gender, diabetes, time on chronic dialysis therapy, and serum albumin. The report indicates that although there was a significant relationship between some of these covariates and mortality, there was no significant treatment by covariate interaction that would help explain the numerical difference in mortality rates. This reviewer believes the purpose of the amendment is to answer a narrower question regarding mortality, viz. is there an overall difference in the mortality rates between the two groups. Also, there doesn't seem to be an adequate amount of information to answer questions about the treatment by covariate interactions. For these reasons, this will not be investigated in further depth in this review.

5. Conclusions

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.

Appendix

This reviewer estimated the proportion of patients in each group that survive and the mortality status is known to the investigator at each time point. In this analysis, a month is defined as (#days from start of study)*12/365. A patient who was known to be alive x number of days from the start of the study (with no further follow-up) is counted as having an event at that time. A patient who died is counted as censored at the time of death. Figure A1 shows the resulting Kaplan-Meier estimates and Table A1 shows the actual numerical estimates for each group. Both the figure and the table illustrate that a relatively high number of patients in each group did not have follow-up for the intended 13-month period. Roughly 40% in the control group and 32% in the Extraneal group did have complete follow-up for this period of time.

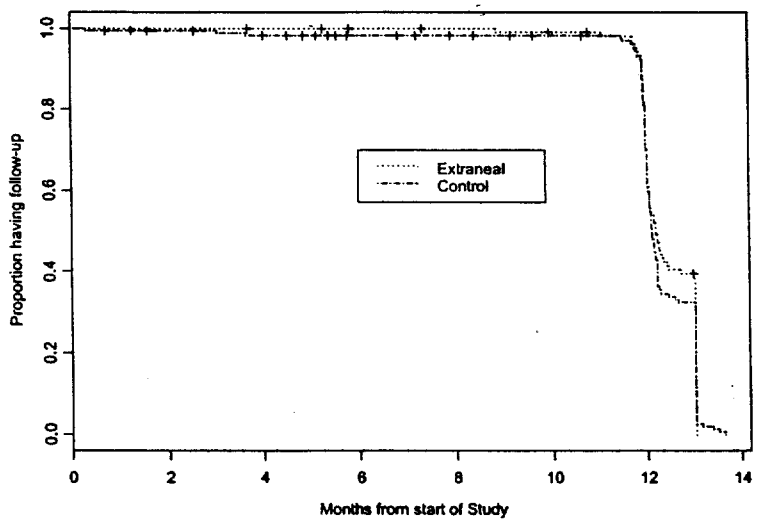

Figure A1. Kaplan-Meier estimates of probability of remaining in study over time. Patients who died are counted as censored in this analysis. Months = Days*12/365.

Table A1. Kaplan-Meier estimates of proportion of patients who survive and the mortality status is known by the investigator.

[redacted]			
Months from start of study	# at risk	# of events	Survival
8.88	108	1	0.991
11.08	105	1	0.981
11.74	104	2	0.962
11.80	102	1	0.953
11.84	100	1	0.943
11.87	99	1	0.934
11.93	97	9	0.847
11.97	88	4	0.809
12.00	84	11	0.703
12.03	73	11	0.597
12.07	62	5	0.549
12.10	57	1	0.539
12.16	56	2	0.520
12.20	54	3	0.491
12.23	51	2	0.472
12.26	49	2	0.453
12.30	47	1	0.443
12.33	46	1	0.433
12.36	45	1	0.424
12.43	44	1	0.414
12.46	43	1	0.404
12.72	42	1	0.395
13.02	40	40	0.000

Table A1 (continued).

[redacted] group			
Months from start of study	# at risk	# of events	Survival
0.329	175	1	0.99429
3.058	170	1	0.98844
3.682	169	1	0.98259
11.507	154	1	0.97621
11.540	153	1	0.96983
11.704	152	1	0.96345
11.770	151	2	0.95069
11.803	149	1	0.94431
11.836	148	2	0.93154
11.901	146	1	0.92516
11.934	145	8	0.87412
11.967	136	9	0.81627
12.000	126	18	0.69966
12.033	108	14	0.60897
12.066	94	8	0.55714
12.099	86	8	0.50531
12.132	78	4	0.47940
12.164	74	5	0.44701
12.197	69	3	0.42757
12.230	66	10	0.36279
12.263	56	1	0.35631
12.296	55	2	0.34335
12.460	53	1	0.33688
12.592	52	1	0.33040
12.658	51	1	0.32392
13.019	50	46	0.02591
13.151	4	1	0.01944
13.381	3	1	0.01296
13.512	2	1	0.00648
13.644	1	1	0.00000

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This review consists of 7 pages of text, tables, and figures.

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