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**APPLICATION NUMBER for: 020182, S006**

**CLINICAL PHARMACOLOGY and  
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**

NDA 20-182/SE1-006

SUBMISSION DATE:

01-DEC-99

BRAND NAME:

Carnitor® Injection

GENERIC NAME:

Levocarnitine 200mg/mL as 2.5mL or 5mL dose ampoules, for intravenous injection

REVIEWER:

Robert M. Shore, Pharm.D.

SPONSOR:

Sigma-tau Pharmaceuticals, Inc.,  
Gaithersburg, MD

TYPE OF SUBMISSION:

BL: Labeling

**SYNOPSIS:**

The sponsor has accepted the labeling changes previously proposed. This submission corrects the data in one table of the proposed labeling. Line 113 of the sponsor's labeling in this submission is acceptable.

There is one error in the labeling which needs to be corrected. Line 112 reads

[redacted] but should read [redacted]

**COMMENTS TO BE SENT TO SPONSOR:**

1) The change to the table starting at line 113 of the proposed labeling is acceptable.

2) There is one error in the labeling which needs to be corrected. Line 112 reads  
[redacted] but should read [redacted]

Robert M. Shore, Pharm.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

[redacted] /S/

03-DEC-99

RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader

[redacted] /S/

12/3/99

CC: NDA 20-182/SE1-006 (orig., 1 copy), HFD-510(Orloff, Hess), HFD-870(Ahn), CDR (Barbara Murphy).

Code: **AE**

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**

<b>NDA 20-182 / SE1-006</b>	<b>SUBMISSION DATE:</b>	<b>29-JAN-99, 15-NOV-99(BB)</b>
<b>BRAND NAME:</b>	<b>Carnitor® Injection</b>	
<b>GENERIC NAME:</b>	<b>Levocarnitine 200mg/mL as 2.5mL or 5mL dose ampoules, for intravenous injection</b>	
<b>REVIEWER:</b>	<b>Robert M. Shore, Pharm.D.</b>	
<b>SPONSOR:</b>	<b>Sigma-tau Pharmaceuticals, Inc., Gaithersburg, MD</b>	
<b>TYPE OF SUBMISSION:</b>	<b>Efficacy Supplement: Labeling for new population</b>	

**TERMS AND ABBREVIATIONS:**

Carnitine and levocarnitine are used interchangeably.

AC..... Acyl-L-carnitine  
ALC..... Acetyl-L-carnitine  
DMEDP..... Division of Metabolic and Endocrine Drug Products  
DPE-2..... Division of Pharmaceutical Evaluation 2  
ESRD..... End stage renal disease  
HD..... Hemodialysis  
IV..... Intravenous  
LC..... Levocarnitine  
OCPB..... Office of Clinical Pharmacology and Biopharmaceutics  
TC..... Total carnitine (includes LC, ALC, AC, and all other carnitine esters)

**SYNOPSIS:**

Kendall McGraw (original sponsor of Carnitor IV) submitted NDA 19-823 on 27-JAN-88 and received an NA letter on 01-FEB-89; the proposed indication was for the treatment of manifestations of secondary carnitine deficiency in patients with end stage renal disease who are on hemodialysis. Biopharm items of deficiency were the lack of 1) bioavailability data (a request for waiver of bioavailability requirement was not granted) and 2) dose-response data. A 1992 submission addressed bioavailability and in December 1992 Carnitor injection was approved for the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency. The current submission (sponsored by sigma-tau, which acquired ownership of NDA 19-823) includes a pharmacokinetic study of levocarnitine in patients with end stage renal disease who require hemodialysis as well as dose-response data.

The studies submitted in Section 6 of this NDA indicate that dosing with 20mg/kg Carnitor after each dialysis (i.e., three times a week) results in elevated LC concentrations. Although two clinical studies dosed patients up to 24 weeks and an intensive pharmacokinetic study dosed patients up to 8 weeks, there is evidence that doses of 10-20 mg/kg for as few as 2 weeks may be adequate therapy; after this, doses can be decreased.

**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-182 / SE1-006 submitted 29-JAN-99 and 15-NOV-99. The overall Human Pharmacokinetic Section is acceptable to OCPB. Labeling comments (p.8) should not be

forwarded to the sponsor since labeling negotiations are already underway and the included comments are not necessarily the latest version of the labeling.

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**BACKGROUND:**

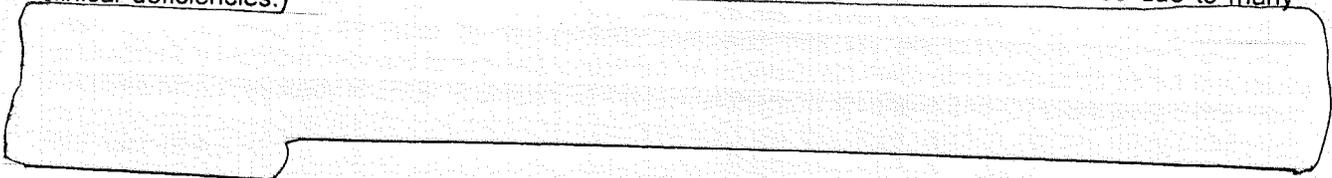
Levocarnitine is an essential endogenous factor in fatty acid oxidation. Deficiencies of levocarnitine, either through primary or secondary (e.g., iatrogenic) causes, can result in adverse effects such as hypotension, muscle weakness, hypoglycemia, neurologic disturbances, or congestive heart failure. Normal plasma concentrations of free carnitine are about 40 to 50  $\mu\text{mol/L}$  ( $\mu\text{M}$ ) although the total pool of carnitine in the body includes a number of esters and most carnitine is located within muscles. Although carnitine exists in some ester forms in the body, the clinically relevant concentration is plasma free carnitine (as per expert consultations in DAVDP MO review of IND [redacted]).

Currently, Carnitor is indicated for primary or secondary levocarnitine deficiency and is available as an oral solution, oral tablet, and IV solution.

End stage renal disease patients on hemodialysis maybe prone to secondary levocarnitine deficiency mostly because of dialytic losses of carnitine and its precursors lysine and methionine. The sponsor is proposing that Carnitor IV solution be indicated for 'the treatment of manifestations of secondary carnitine deficiency in patients with end stage renal disease who require hemodialysis'.

According to this submission, levocarnitine is approved for the treatment of secondary carnitine deficiency in hemodialysis patients in a number of foreign countries. Also, the sponsor claims that 'in the US, the current sales of Carnitor Injection for hemodialysis are approximately 80% of the total Carnitor Injection sales' and that certain Medicare groups recommend its use in HD for ESRD.

Historically, on 27-JAN-88, NDA 19-823 for VitaCarn (20% levocarnitine injection) was submitted with this same indication by Kendall McGraw. Carnitor (levocarnitine) qualified for orphan designation for the treatment of manifestations of carnitine deficiency in patients with end stage renal disease who require dialysis on 06-SEP-88. A 'Not Approvable' letter for NDA 19-823 was issued 01-FEB-89 due to many clinical deficiencies.



On 27-JUN-91 Kendall McGraw withdrew the NDA. Sigma-tau acquired ownership of NDA 19-823 on 02-JUL-92.

On an addition historic note, and pertinent to labeling, submissions dated 11-FEB-91 and 27-AUG-92 for NDA 18-948/S-009 (oral solution and tablet), and 26-APR-91 and 23-APR-92 for NDA 20-182 were made by Sigma-tau; the reviewer was John Hunt. The submission contained labeling and a study which 1) characterized the pharmacokinetics of IV levocarnitine in healthy adults, 2) demonstrated that the absolute bioavailability of the three oral dosage forms tested (solution, tablet, unapproved chewable tablet) is about 15%, and 3) demonstrated bioequivalence between the three oral dosage forms. This study seems to be the basis for the referenced publication by Sahajwalla (1995).

Study P01666 (The pharmacokinetics of VitaCar® [20% levocarnitine injection] in patients with end stage renal disease on hemodialysis) will not be reviewed because no assay validation or subject data are included and, as per the sponsor, "A systematic complete pharmacokinetic analysis of the data was...carried out neither by the Investigator nor by the Sponsor. [A] specific pharmacokinetic study (ST-198-US-96-PK01) (was) recently completed" and is included in this submission.

### STUDY SUMMARY INDEX

Protocol Number	Title	Page
ST-198-US-96-PK01	Pharmacokinetics of L-carnitine following single and multiple intravenous administration of 20mg/kg Carnitor® in chronic hemodialysis patients with end stage renal disease	p. 33
ST-96001	Safety and efficacy of levocarnitine supplementation in end stage renal disease patients undergoing maintenance hemodialysis: a multi-center study, dose-ranging study	p. 43
ST-96002	Levocarnitine supplementation to improve exercise performance and quality of life in patients with end stage renal disease (ESRD) undergoing maintenance hemodialysis: a phase III, multi-center study	p. 43

### DRUG FORMULATION:

Carnitor injection is a sterile aqueous solution of 200mg levocarnitine (Figure 1) in 1mL solution. The pH is adjusted to 6.0 to 6.5 with HCl.

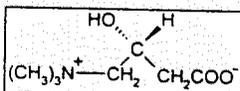
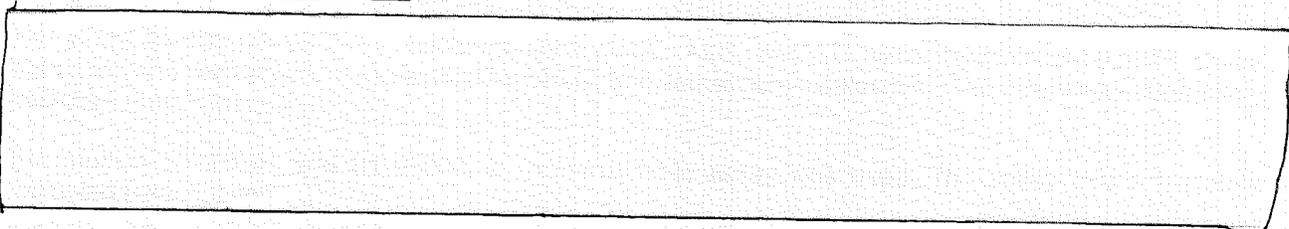


Figure 1. levocarnitine.

### ANALYTICAL METHODOLOGY:



## HUMAN PHARMACOKINETICS:

### A. *Single vs. Multiple Dose Administration in patients on HD in ESRD*

Study ST-198-US-96-PK01 evaluated the pharmacokinetics of LC, ALC, and TC at baseline and after single and multiple dose IV administration of 20mg/kg of Carnitor (Note: The primary clinical parameter used to follow patients is the LC concentration; the ALC and TC are not clinically useful). Twelve chronic HD patients with ESRD who had not received LC previously were enrolled. These patients were receiving maintenance HD for a minimum of 6 months, were in stable medical condition, had not received carnitine, and had an AC/LC plasma ratio of more than 0.4 which is associated with carnitine deficiency.

The current labeling suggests that an AC/LC ratio above 0.4 is associated with LC deficiency. The Medical Officer has indicated, in personal conversation, that this ratio is probably less clinically relevant than actual LC concentrations. The plasma AC/LC ratios are summarized in Figure 2. The mean value shows relative stabilization by week 4 (2 weeks of Carnitor therapy). Although some ratios drop below 0.4 over the course of the 8 weeks of Carnitor therapy, most remain above 0.4 throughout the 8 weeks of therapy.

Plasma concentrations of LC rise quickly after initiation of Carnitor therapy and remain elevated above the normal range of 40-50 $\mu$ mol/L (Figure 3). After about Week 4 (2 weeks of Carnitor therapy), plasma LC concentrations attain near-plateau concentrations well above normal. The clinical need for such elevated concentrations of LC is unknown and the safety issues, if any, surrounding these elevated LC concentrations should be addressed by the Medical Officer.

Studies ST-96001 and ST-96002 were both of similar design: multicenter, randomized, double-blind, placebo-controlled clinical trials. Patients with ESRD on thrice weekly HD received either placebo, 10, 20, or 40 mg/kg Carnitor (ST-96001) or placebo or 20 mg/kg (ST-96002) after each dialysis. In addition to the primary clinical endpoints of VO<sub>2</sub> max and Quality of Life, a single plasma sample for LC, ALC, and TC was obtained at baseline, week 12, and week 24 prior to HD.

Table 1 summarize the AC/LC ratio data for study ST-96001. The 10mg/kg dose seems to have the greatest impact on reducing this ratio while the placebo and 40 mg/kg doses have no apparent effect. The 20 mg/kg dose reduces the ratio at 12 weeks but then the ratio rebounds at 24 weeks to an intermediate value.

Table 2 summarize the AC/LC ratio data for study ST-96002. The 20 mg/kg dose reduces the ratio at 12 weeks and further reductions are seen at 24 weeks. However, it is interesting to note that the placebo patients also had similar decreases in their AC/LC ratios for unknown reasons.

Tables 3 and 4 indicate that LC concentrations are elevated at 12 weeks of Carnitor therapy. Even 10mg/kg produces substantially elevated LC concentration of 116  $\mu$ mol/L at 12 weeks. The two studies have similar results in the 20mg/kg group at both 12 and 24 weeks. Also, these tables indicate that LC concentrations continue to rise between 12 and 24 weeks of Carnitor therapy. Levocarnitine concentrations in patients receiving only placebo remain at baseline concentrations (below normal) throughout the 24 weeks.

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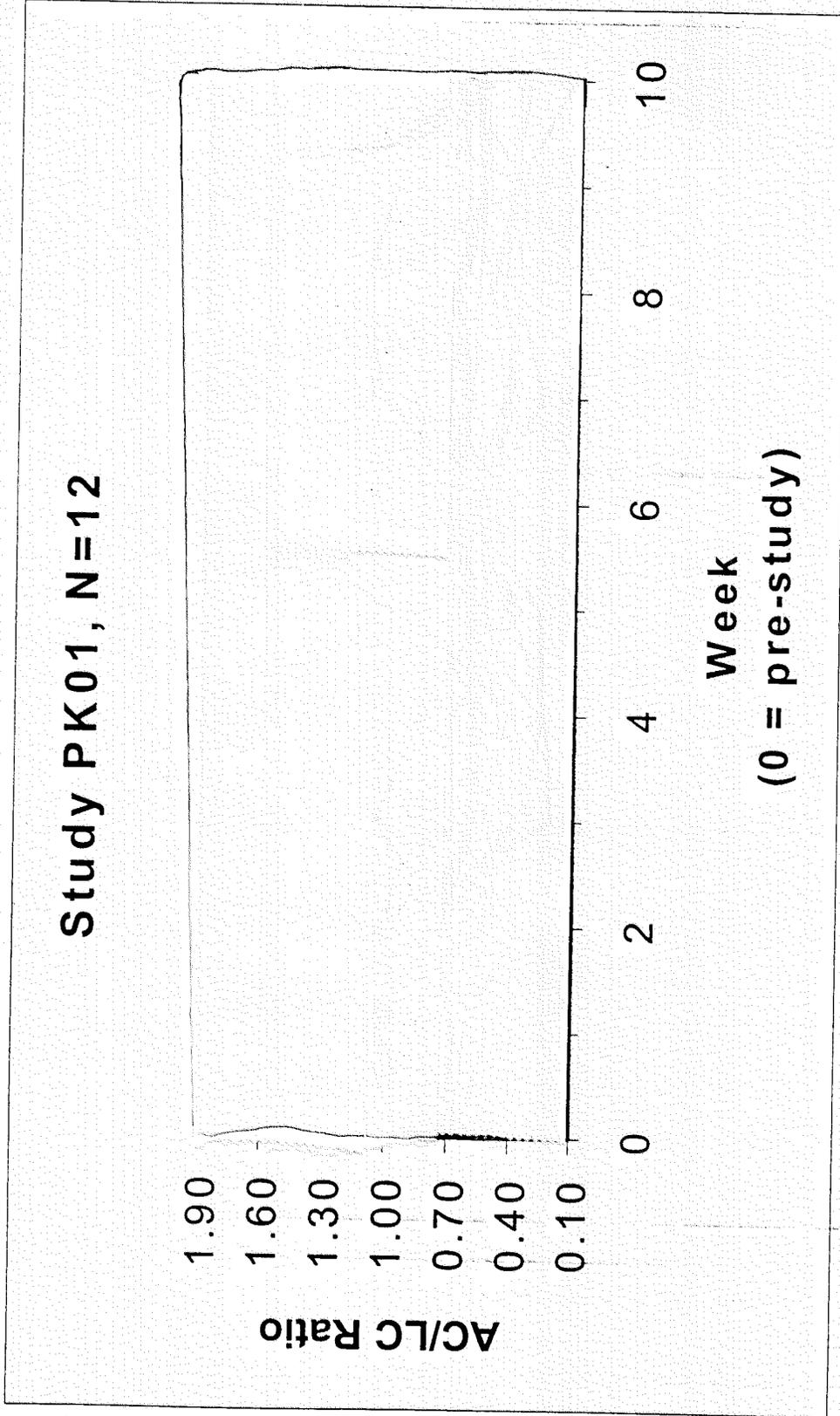


Figure 2. AC/LC ratios before HD. Dosing started at week 2. Thin lines are individual data, thick line is mean data.

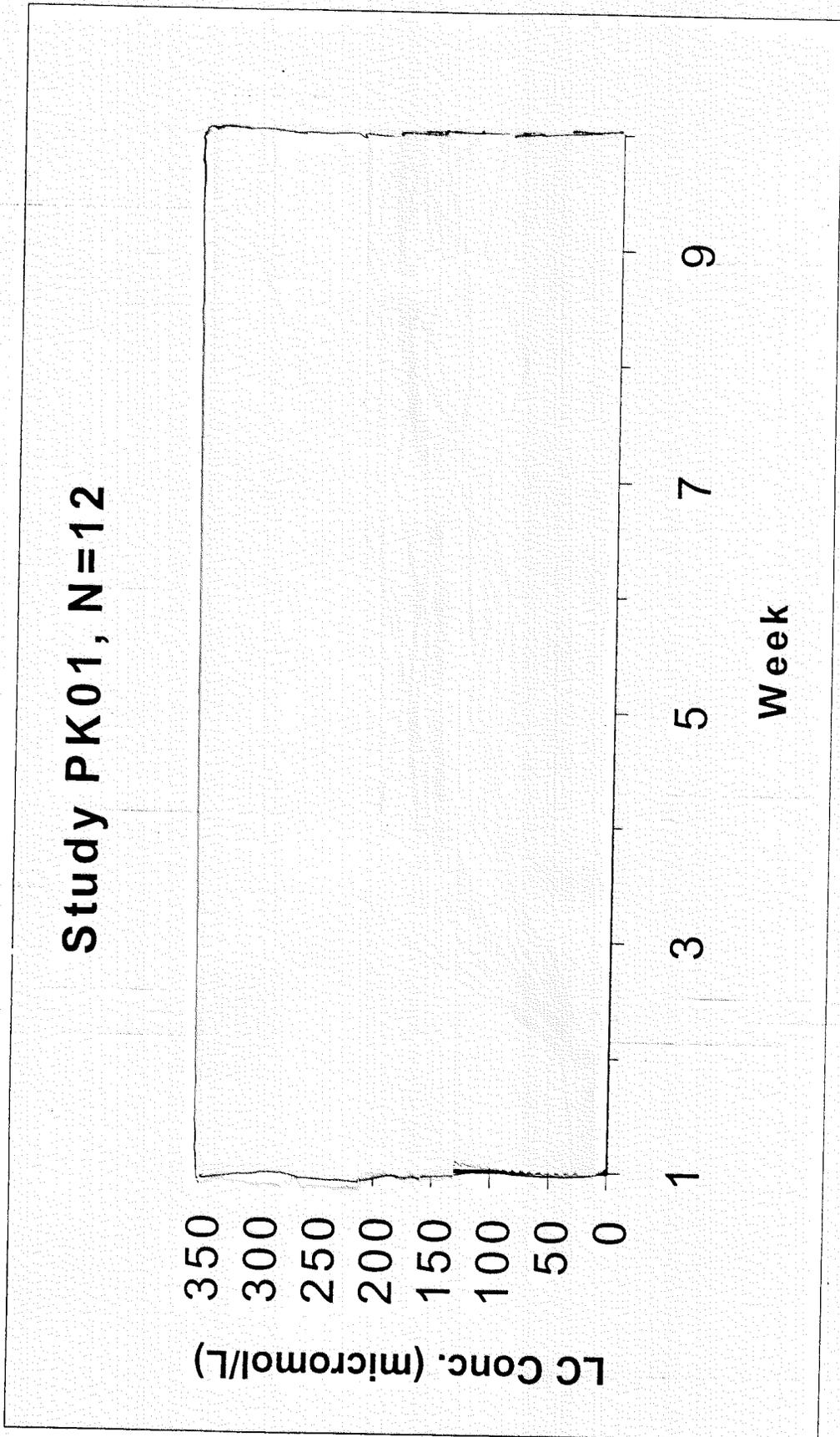


Figure 3. LC concentrations before HD. Dosing started at week 2. Thin lines are individual data; thick line is mean data.

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Table 1.

Protocol ST-96001: Mean Pre-Dialysis Plasma Acylcarnitine/L-Carnitine Ratio

	Placebo			10 mg/Kg			20 mg/Kg			40 mg/Kg		
	Initial	Week 12	Week 24	Initial	Week 12	Week 24	Initial	Week 12	Week 24	Initial	Week 12	Week 24
Mean	0.81	0.80	0.77	0.92	0.63	0.54	0.77	0.54	0.67	0.81	0.78	0.83
Std	0.31	0.35	0.53	0.30	0.28	0.35	0.47	0.25	0.34	0.35	0.44	0.64
Min	0.11	0.15	0.22	0.48	0.12	0.24	0.32	0.06	0.19	0.31	0.20	0.11
Max	1.78	1.56	2.40	1.78	1.36	1.67	2.77	1.17	1.86	2.01	1.95	3.08
N	33	32	30	34	30	28	32	30	28	33	30	29

Table 2.

Protocol ST-96002: Mean Pre-Dialysis Plasma Acylcarnitine/L-Carnitine Ratio

	Placebo			20 mg/Kg		
	Initial	Week 12	Week 24	Initial	Week 12	Week 24
Mean	0.84	0.73	0.63	0.82	0.70	0.61
Std	0.43	0.20	0.29	0.22	0.27	0.29
Min	0.40	0.43	0.19	0.50	0.08	0.17
Max	2.66	1.12	1.65	1.42	1.29	1.27
N	30	27	27	30	25	23

Table 3.

Protocol ST-96001  
Pre-Dialysis Plasma Concentration of L-Carnitine, Total Carnitine, and Acetyl-L-Carnitine  
Laboratory Test: L-Carnitine (Serum Free) Test Units: nmol/ml =  $\mu\text{mol/L}$

TREATMENT GROUP		VISIT		
		Initial	Week 12	Week 24
Placebo	N	33	32	30
	MEAN	24.43	28.93	27.63
	MEDIAN	23.50	24.65	26.40
	STD	7.02	21.01	11.39
	MIN	14.00	12.80	10.70
	MAX	39.90	132.00	58.00
L-Carn 10 mg	N	34	30	28
	MEAN	22.26	115.58	148.36
	MEDIAN	21.70	105.00	147.00
	STD	9.13	69.41	50.45
	MIN	8.00	49.10	75.60
	MAX	51.20	441.00	248.00
L-Carn 20 mg	N	32	30	28
	MEAN	25.30	209.57	240.32
	MEDIAN	25.50	199.00	236.00
	STD	8.71	56.44	60.42
	MIN	9.31	118.00	120.00
	MAX	49.70	326.00	384.00
L-Carn 40 mg	N	34	30	29
	MEAN	23.65	371.13	455.52
	MEDIAN	25.10	368.50	453.00
	STD	8.71	111.34	161.65
	MIN	7.50	124.00	183.00
	MAX	41.80	638.00	770.00

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Table 4.

TREATMENT GROUP		VISIT		
		Initial	Week 12	Week 24
Protocol ST-96002 Pre-Dialysis Plasma Concentration of L-Carnitine, Total Carnitine, and Acetyl-L-Carnitine Laboratory Test: <u>L-Carnitine</u> (Serum Free) Test Units: nmol/ml = $\mu\text{mol/L}$				
Placebo	N	30	27	27
	MEAN	23.70	27.05	27.63
	MEDIAN	21.10	25.10	24.50
	STD	8.93	10.51	11.25
	MIN	13.20	10.50	7.78
	MAX	61.90	53.10	54.90
L-Carn 20 mg	N	30	25	23
	MEAN	27.12	189.47	243.43
	MEDIAN	26.70	194.00	237.00
	STD	6.36	69.99	75.84
	MIN	17.50	70.90	107.00
	MAX	41.70	394.00	471.00

**B. Dose and Dosage Form Proportionality**

From study ST-96001 the sponsor claims that

'plots of pre-dialysis concentrations of LC, ALC, and TC at week 12 and 24 against the dose of Carnitor show a linear dose-response relationship. This linearity suggests that dialysis clearance is dose-independent between 0 and 40 mg/kg of Carnitor.'

Neither these plots nor any statistical analysis were found in Section 6 of this submission. However, using the mean data there seems to be slightly less-than-proportional increases in the pre-dialysis LC (See Table 3) and TC concentrations at both 12 and 24 weeks and more-than-proportional increases in the pre-dialysis ALC at week 24 with increasing dose. Thus, the statement that there is dose-linearity is probably not accurate.

**DISCUSSION:**

Carnitor therapy does increase LC concentrations in plasma in patients with ESRD on HD. The intensive pharmacokinetic study indicates that after only two weeks of 20mg/kg Carnitor therapy the mean LC concentration is approximately 150  $\mu\text{mol/L}$  and the AC/LC ratio is stable. Study ST-96001 indicates that after 12 weeks of Carnitor 20mg/kg therapy the mean plasma LC concentration is 210  $\mu\text{mol/L}$ ; with 10mg/kg the mean plasma LC concentration is 116  $\mu\text{mol/L}$  at 12 weeks. This indicates that elevated concentrations are achieved relatively quickly with 20mg/kg Carnitor and possibly 10mg/kg Carnitor would be an adequate dose to elevate LC in ESRD patients on HD; after a few weeks of 10-20mg/kg Carnitor it may be possible to decrease the dose based on LC concentrations.

**LABELING COMMENTS:**

Strikeout text is being proposed for removal from labeling; underlined text is being proposed for addition to labeling;  indicates an FDA comment/explanation only and is not intended to be included in the labeling.

11 Pages

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LABELLING

Robert M. Shore, Pharm.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

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30-NOV-99

RD initialed by Hae-Young Ahn, Ph.D., Team Leader J.Hunt 30-NOV-99

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/

11/30/99

CC: NDA 20-182/SE1-006 (orig.,1 copy), HFD-510(Hess, Orloff, Herman), HFD-870(Ahn, ChenME),  
HFD-850(Lesko, Huang) CDR (Barbara Murphy).

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**Appendix 1. Proposed Draft Labeling**

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## Appendix 2. Study summaries

Study ST-198-US-PK01

Title: Pharmacokinetics of L-carnitine following single and multiple intravenous administration of 20mg/kg Carnitor® in chronic hemodialysis patients with end stage renal disease

Vol: 2-5

Date of Report: Jan 1999

Study Period: 26-NOV-97 to 21-OCT-98

Sample Analysis Period: 30-JUN-98 to 16-NOV-98

Objectives:

1. Evaluate pharmacokinetics of LC following single and multiple IV doses of 20 mg/kg in hemodialysis patients with ESRD;
2. Determine the effects of Carnitor administration on plasma levels of ALC and TC (which includes LC, ALC and all other carnitine-esters).

Design:

Single and multiple dose, three-period study. Twelve patients (6 male) with ESRD, undergoing HD for at least 6 months and receiving bicarbonate dialysis treatment three times a week, were enrolled. The pharmacokinetics of LC, ALC, and TC were evaluated first under baseline conditions with saline administration (endogenous pharmacokinetics); second, after a single dose of Carnitor (20 mg/kg IV after HD); and third, after 10 weeks of repeated Carnitor administration (20 mg/kg IV after each HD session). The study also included a 6 week washout period. In each period, the disposition of LC, ALC, and TC was studied during the intra-dialysis (simultaneous venous and arterial blood and dialysis fluid collection during HD) and inter-dialysis (venous blood collection for 44 hours after saline or drug administration) period. Also, pre- and post-dialysis venous blood samples were collected at the second dialysis session of each study week.

Population/Demographics:

Demographics are presented in the following table. These were ambulatory outpatients on HD for a minimum of 6 months and in stable clinical condition. Six patients participated in the 6-week washout period.

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