sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

HAND DELIVERED

NDA 20-182
Carnitor® (levocarnitine) Injection
S-006

December 13, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Attention: Document Control Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and our recent supplement (S-006) providing for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with End Stage Renal Disease who are on hemodialysis. Also, please refer to our submission of December 3, 1999 wherein we provided revised draft labeling in response to the Agency's request of December 3, 1999.

In addition, please refer to a December 13, 1999 telephone conversation between Ms. Maureen Hess of the Agency and Gianfranco Fornasini, Ph.D. of Sigma-Tau, wherein Ms. Hess requested that we change the How Supplied section (lines 275-278) for consistency of the draft labeling submitted on December 3, 1999.

DESK COPY
A/S Maureen Hess

Submitted herewith, in duplicate, please find the revised labeling with the requested changes.

In addition, we are providing a diskette containing the revised labeling. The file entitled pi_121399.doc is an electronic copy of the revised draft prescribing information in

We certify that the diskette provided in each copy of this submission is virus-free. The software used to scan for viruses was The date of the last update was December 6, 1999, prior to the creation of this diskette.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 670-2192.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

cc: Ms. Maureen Hess

APPEARS THIS WAY
ON ORIGINAL

SCR-006-DL

sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

HAND DELIVERED

NDA 20-182
Carnitor® (levocarnitine) Injection
S-006

December 3, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Attention: Document Control Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
INITIALS DATE

Response to FDA Request

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and our recent supplement (S-006) providing for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with End Stage Renal Disease who are on hemodialysis. Also, please refer to our submission of December 1, 1999 wherein we provided revised draft labeling in response to the Agency's request of November 29, 1999.

In addition, please refer to a December 3, 1999 telephone conversation between Ms. Maureen Hess of the Agency and Judith A. Inge of Sigma-Tau, wherein Ms. Hess requested that we correct line 112 of the draft labeling submitted on December 1, 1999 from [redacted]

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Submitted herewith, in duplicate, please find the revised labeling with the requested change.

In addition, we are providing a diskette containing the revised labeling. The file entitled pi_120399.doc is an electronic copy of the revised draft prescribing information in [redacted]

We certify that the diskette provided in each copy of this submission is virus-free. The software used to scan for viruses was [redacted] The date of the last update was November 22, 1999, prior to the creation of this diskette.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 670-2192.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

cc: Ms. Maureen Hess

sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

HAND DELIVERED

NDA 20-182
Carnitor® (levocarnitine) Injection
S-006

December 1, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Attention: Document Control Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and our recent supplement (S-006) providing for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with End Stage Renal Disease who are on hemodialysis. Also, please refer to a November 29, 1999 facsimile from the Agency wherein requested revisions to our draft labeling initially submitted with S-006 were provided.

In addition, please refer to a November 29, 1999 telephone conversation between Ms. Maureen Hess of the Agency and Edward F. Lemanowicz, Ph.D. and the undersigned of Sigma-Tau, wherein we clarified the submission requirements for the response to the labeling revisions.

DESK COPY
Ms. Maureen Hess

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Submitted herewith, in duplicate, please find the revised labeling. All of the requested changes have been made with the exception of the single dose trough value in the table in previous line 152, new line 113. The value that was suggested (105 ± 40) has been changed to 68.4 ± 26.1 based on Volume 2 of the initial SNDA, page 000240, Table 3.2.3. The value suggested was probably derived from page 000080 of Volume 2, where the value of 105 represents the trough, pre-dialysis 2 week 3, before the fourth dose. In fact, the first dose was given after dialysis 2 week 2, the second dose was given after dialysis 3 week 2, and the third dose was given after dialysis 1 week 3. Therefore, the value "68.4" represents the trough, pre-dialysis 3 week 2, pre-dose 2 (after the single dose).

In addition, please note that since certain references were deleted the reference numbers provided in your requested draft have been changed as follows:

- Reference 10 has been deleted per your comment on previous line 132
- Reference 11 in previous line 194 has been changed to 10 due to the deletion of previous reference 10
- References 12, 13, 14, 15, 16 and 17 have been deleted per comments on lines 239-251.

In addition, we are providing a diskette containing the revised labeling. The file entitled pi_113099.doc is an electronic copy of the revised draft prescribing information in Microsoft® Word 97 SR-2. The file entitled pi_113099_6.doc is an electronic copy of the revised draft prescribing information in [redacted]

We certify that the diskette provided ~~in each copy of this submission~~ is virus-free. The software used to scan for viruses was [redacted] The date of the last update was November 22, 1999, prior to the creation of this diskette.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 670-2192.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

cc: Ms. Maureen Hess

sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

NDA SUPP AMEND
SE1-006-BB

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

NDA 20-182
Carnitor® (levocarnitine) Injection
S-006

November 15, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Attention: Document Control Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and our recent supplement (S-006) providing for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with End Stage Renal Disease who are on hemodialysis. Also, please refer to a November 12, 1999 phone inquiry by Dr. Robert Shore of the Agency to the undersigned regarding the pharmacokinetic analysis of Study ST198-US96-PK01.

Based on Dr. Shore's review of Volume 2, page 000248, Table 3.31 - L-carnitine plasma concentrations and page 000249, Table 3.32 - acetyl-L-carnitine plasma levels, he has calculated that the acetyl/levocarnitine ratio at pre-screening drops before carnitine therapy to less than 0.4 during one week. He asked for clarification.

In addition, Dr. Shore requested calculation of the mean ratio for clinical studies ST-96001 and ST-96002. He asked for a graph of mean ratios for the patients at initial, week 12, and week 24. To assist us, he faxed an example of the graph that he prepared on Study ST198-US96-PK01.

In addition, please refer to a subsequent call on November 12, 1999 wherein Gianfranco Fornasini, Ph.D., Director, Regulatory Sciences and Pharmacokinetics, Sigma-Tau Pharmaceuticals, Inc., and the undersigned addressed Dr. Shore's inquiry.

Dr. Fornasini noted that the values reported in the chart faxed by Dr. Shore were based on acetyl carnitine/levocarnitine ratios rather than an acylcarnitine/levocarnitine ratio, as defined in the supplement. The difference between acetyl and acylcarnitine are defined in Volume 4, pages 000039-000040, Section 6.36 and 6.37.

Dr. Shore asked that we submit a chart of individual ratios of the Study ST198-US96-PK01.

In addition, he requested the following: 1) Clinical Study ST-96001 - four graphs dealing with the mean ratio for acylcarnitine/levocarnitine for placebo and for each treatment group (10, 20 and 40 mg/Kg); 2) Clinical Study ST-96002 - two graphs for the placebo and 20 mg/Kg treatment groups; 3) Combined Clinical Studies ST-96001 and ST-96002 - a graph of the 20 mg/Kg treatment groups.

In response to this request submitted herewith, in duplicate, are the following tables and graphs:

Attachment 1: Tables of mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST-96001, ST-96002 and ST-96001/ST-96002 combined.

Attachment 2: Graphs of mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST-96001.

Attachment 3: Graphs of mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST-96002.

Attachment 4: Graphs of mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST-96001/ST-96002 combined.

Attachment 5: Table of individual and mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST198-US96-PK01.

Attachment 6: Graphs of individual and mean pre-dialysis plasma acylcarnitine/L-carnitine ratios for ST198-US96-PK01.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 670-2192.

Sincerely,

FOR

A.C. Hanzas
Director, Regulatory Affairs

cc: Dr. Robert Shore (via express mail)

REVIEWS COMPLETED

DATE

sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

NDA S-006

NDA 20-182
Carnitor® (levocarnitine) Injection
S-006

November 5, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Attention: Document Control Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and our recent supplement (S-006) providing for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with End Stage Renal Disease who are on hemodialysis. Also, please refer to a November 4, 1999 phone inquiry by Dr. Robert Shore of the Agency to the undersigned and Gianfranco Fornasini, Ph.D., Director, Regulatory Sciences and Pharmacokinetics, Sigma-Tau Pharmaceuticals, Inc., and Edward F. Lemanowicz, Ph.D., Vice President, Regulatory Sciences, Sigma-Tau Pharmaceuticals, Inc., regarding the analytical method validation for the carnitine assay methods employed in Study ST-96001 and ST-96002. In addition, please refer to a subsequent call on November 4, 1999 wherein Dr. Fornasini and Dr. Lemanowicz addressed Dr. Shore's inquiry and wherein Dr. Shore requested that we confirm our response in writing in addition to providing the standard concentrations of the calibration curves for the assay validation reports.

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In response to this request submitted herewith, in duplicate, is the table with the standard concentrations of the calibration curves for the carnitine assay method employed in Study ST-96001 and ST-96002. These standard concentrations are derived from Table 1 (pages 000232-000233) and Table 1 (pages 000260-000261) of volume 6 of the NDA 20-182, Supplement S-006, dated January 29, 1999.

We also confirm that the limits of quantification provided with validation report BAR MCG 96-001 and 96-002 do not represent the limits of quantification of the calibration curves, instead they are the ranges of the plasma levels of the L-carnitine (LC), acetyl-L-carnitine (ALC) and total carnitine (TC) measured in the plasma samples of the patients.

The ranges of the calibration curves ranged from 7.50 to 84.4 nmol/mL for LC, from 0.652 to 9.78 nmol/mL for ALC, and from 7.81 to 93.8 nmol/mL for TC. These ranges never changed and were used for the analysis of all the plasma samples of the two clinical trials.

Plasma samples with concentrations above the upper limits of the calibration (84.4, 9.78 and 93.8 nmol/mL for LC, ALC and TC, respectively) were diluted appropriately prior to assay in order to fit them in the range of quantification of the calibration

If you have any questions regarding this submission, do not hesitate to contact me at (301) 670-2192.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

cc: Dr. Robert Shore (via facsimile)

000002

sigma-tau
PHARMACEUTICALS, Inc.

800 south frederick avenue
gaithersburg, md 20877

telephone: (301) 948-1041

telefax:
Sales & Marketing (301) 948-3194
General Administration (301) 948-1862
Clinical/Medical (301) 948-3679
Regulatory (301) 948-8627

SUPPL NEW CORRESP
SE1-006
SNC

October 14, 1999

BY FASCIMILE/CONFIRMATIONB COPY TO FOLLOW

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA No. 20-182 (S-006); Carnitor® Injection (levocarnitine)

Dear Dr. Sobel:

Please refer to our supplemental New Drug Application (sNDA) for Carnitor® Injection (levocarnitine) No. 20-182 (S-006) submitted on January 29, 1999, which is currently under review in your Division.

The purpose of this correspondence is to authorize our regulatory counsel, Hyman, Phelps & McNamara, P.C., to communicate both formally and informally with you on matters concerning our sNDA. This authorization includes any written submission to the sNDA file on behalf of Sigma-Tau Pharmaceuticals, Inc.

Sincerely,

C. Kenneth Mehrling

C. Kenneth Mehrling
General Manager

Cc: Frank J. Sasinowski, Esq.
Hyman, Phelps & McNamara, P.C.

LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329

2603 MAIN STREET
SUITE 650
IRVINE, CALIFORNIA 92614-4260
(949) 553-7400
FACSIMILE
(949) 553-7433

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NDA SUPP AMEND
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BL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 12 1999
HFD-510

October 8, 1999

BY FACSIMILE/CONFIRMATION COPY BY MAIL

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA No. 20-182 (S-006); Carnitor® Injection (levocarnitine)

Dear Dr. Sobel:

As you are aware, review of the sNDA for Carnitor® Injection for treatment of manifestations of carnitine deficiency in patients with ESRD who require dialysis is currently underway in the Division. Carnitor® Injection is already approved for "the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency." While I appreciate that an approvability decision has not yet been made for the sNDA, it appears appropriate to open discussions regarding the proposed labeling changes submitted in the sNDA. The purpose of this correspondence is to delineate the two labeling possibilities that we discussed during our September 17th conversation. The possibilities we briefly discussed are listed below as Option 1 and Option 2. Option 1 reflects the labeling as approved in the United Kingdom, while Option 2 is a modification of that as proposed in the sNDA and is documented and supported in the sNDA.

The options follow with possible new language presented in italics.

Option 1: Modify the Indications section of the label to include a "stand-alone" ESRD indication as was done by the Medicines Control Agency (MCA) in the UK labeling:

> For the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency.

Option 2: Expand the Indications section of the label to include both inborn errors of metabolism and ESRD as conditions that may lead to secondary carnitine deficiency.

In both of the above options, the Dosage and Administration section of the label uld also have to be modified. A draft of that text appears below.

CARNITOR® Injection is administered intravenously.

In our September 17th conversation, you indicated an initial, informal preference for Option 1. This proposed change to the Indications section of the label is identical to that adopted in 1994 by the upon approval of Carnitor® for treatment of ESRD patients on dialysis (copy enclosed). Importantly, that approval was based on a far more limited data set than that in the sNDA currently under review. However, Sigma-Tau would accept this labeling if FDA would consider this presentation more appropriate.

The second option was discussed at a meeting we had with the Office of Orphan roduct Development (OOPD) a month ago. At that meeting, Drs. Haffner and IcCormick indicated that OOPD today may not recognize a discreet orphan drug esignation for secondary carnitine deficiency resulting from dialysis of ESRD patients ecause they would consider that to be subsumed within secondary carnitine deficiency. he two indication statements in Option 2 are consistent with the view that secondary arnitine deficiency can result from a number of conditions, of which dialysis of ESRD atients is one.

Additionally, Sigma-Tau is also considering the data it has which may be the basis or six months of pediatric exclusivity in order to extend the orphan drug exclusivity for his product, which now is set to expire on December 16, 1999. We will contact you in the ıear future to discuss our options in this regard.

Should you have any questions or wish to begin discussions for labeling changes consistent with the sNDA data please telephone me at (202) 737-4287 or A.C. Hanzas at Sigma-Tau at (301) 948-1041.

Sincerely,

Frank J. Sasinowski

FJS/dng
Enclosure
7904.001.01

cc: Dr. M. Haffner, OOPD
Mr. A.C. Hanzas, Sigma-Tau

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE