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NDA SUPP AMEND
SNC

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August 27, 1999

Maureen Hess
Food and Drug Administration
5600 Fishers Lane
HFD-510
Rockville, MD 20857

RE: NDA 20-182 Supplement S-006

Dear Ms. Hess:

This will confirm our telephone conversation of August 26, 1999 in which I advised that the following personnel of Sigma-Tau Pharmaceuticals, Inc., U.S.A. are authorized to contact the Division regarding supplement S-006 to NDA 20-182 which provides for a revised indication to include the treatment of manifestations of carnitine deficiency in patients with end stage renal disease who are on hemodialysis:

Edward F. Lemanowicz, Ph.D
Vice President, Regulatory Science

A.C. Hanzas
Director, Regulatory Affairs

In addition, Mr. Frank Sasinowski of Hyman, Phelps and McNamara, P.C., Washington D.C. is authorized to contact the Division in our behalf on issues or questions which may arise relating to orphan drug designation and exclusivity in connection with supplement S-006 to NDA 20-182.

If you have any questions regarding the above please do not hesitate to contact me at 301-670-2192 ex: 192.

Sincerely,

A.C. Hanzas

A.C. Hanzas

cc: NDA 20-182

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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HAND DELIVERED

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

June 23, 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. In addition, please refer to our supplement of January 29, 1999, to NDA 20-182 (S-006) which provided 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 the June 8, 1999, telephone call between Dr. Jim Gebert of the Agency and Mr. A.C. Hanzas of sigma-tau wherein Dr. Gebert requested electronic data files of individual laboratory values for BUN, creatinine, phosphorous and hematocrit, individual demographic data and individual carnitine levels for Protocols P00835, ST-96001 and ST-96002.

DESK COPY:

Ms. Maureen Hess

Submitted herewith, in duplicate and in response to the above referenced request are the following.

- Diskette containing the requested data (individual laboratory values for BUN, creatinine, phosphorous and hematocrit, individual demographic data and individual carnitine levels for Protocols P00835, ST-96001 and ST-96002). In addition, modified data sets for Protocol ST-96001 and Protocol ST-96002 carnitine data are provided due to changes in data at single time points for five patients (see bullet 4 below).

- Paper printout of the individual subject data listings, data dictionaries and contents listings for each data set provided.

- Replacement pages for the Protocol P00835 Reanalysis, which was provided in Volume 15 of the initial S-006 supplement of January 29, 1999. These replacement pages are necessitated by an error in transcribing data from one table to another (Table 17.1) and by a programming error (Tables 12.1 - 12.4 and Appendices 13.1 - 13.3). These replacement pages do not affect our conclusions nor do they affect the SAS data files.

- Replacement pages for the analysis of ST-96001 carnitine blood level data and for the combined analysis of ST-96001/ST-96002 carnitine blood level data. These analyses were submitted in both Volume 6 (Item 6, Pharmacokinetics) and Volume 14 (Item 8/10 Clinical/Statistical) of the initial S-006 supplement of January 29, 1999. These replacement pages are necessitated by changes in individual data for four patients in Protocol ST-96002 at one time point each. These changes were made to the SAS data set for carnitine data for Protocol ST-96001 because of data clarifications from the analysis laboratory. In addition, a change was made to the screening number of one patient in Protocol ST-96002. This change had no effect on the analysis tables. Accordingly, updated data sets as well as the original data sets are provided as part of this submission.

Each item provided is discussed in further detail below.

Diskette

The diskette, which is provided in Attachment 1, contains an ASCII text file named README.TXT that describes the contents of the diskette. A printout of this document is also provided in Attachment 1. The diskette also contains all of the requested SAS data

files and SAS programs to create temporary SAS format libraries. These files are all in SAS version 6.12 for Windows. The SAS files for each study are each in a separate directory and use a standardized naming convention. Please note that carnitine data is provided as part of the lab data set for Protocol P00835, while it is in separate data sets for Protocols ST-96001 and ST-96002. In addition, modified data sets for Protocol ST-96001 and Protocol ST-96002 carnitine data are provided due to changes in data at single time points for four patients and in the screening number for one patient. For Protocol ST-96001 and Protocol ST-96002 carnitine data, we are providing the data sets used in the initial SNDA as well as the updated data sets. All other data sets provided are the same as those used for the analyses submitted in the initial SNDA.

The files for the Protocol P00835 Reanalysis are in the P00835 directory and are as follows:

- DEMO.SD2 SAS data file of Demographic Data
- LAB.SD2 SAS data file of Lab Data (BUN, Creatinine, Inorganic Phosphorus, Hematocrit, Carnitine)
- FORMATS.SAS SAS program to create temporary SAS format library

The following files for Protocols ST-96001 and ST-96002 are in the ST96001 and ST96002 directories, respectively:

- DEMO.SD2 SAS data file of Demographic Data
- LAB.SD2 SAS data file of Lab Data (BUN, Creatinine, Inorganic Phosphorus, Hematocrit)
- FORMATS.SAS SAS program to create temporary SAS format library

The carnitine data files used for the initial supplement are in the subdirectory ORIGINAL in each protocol directory, ST96001 and ST96002. The revised carnitine data files are in the subdirectory UPDATE in each protocol directory. The file name for each of these four data files is as follows:

- CARN.SD2 SAS data file of Lab Data (Carnitine)

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

Paper printout

For each electronic data file provided, i.e., demographics, laboratory data, carnitine data, we are providing paper printouts of the data dictionary, contents listing, and subject data listing. These printouts are organized by protocol and by data set. Within each data set, they are arranged in the following order: data dictionary, contents listing, subject data listing.

Printouts for Protocol P00835 are provided in Attachment 2 as follows:
- Demographics
- Laboratory Data (BUN, Creatinine, Inorganic Phosphorus, Hematocrit, Carnitine)

Printouts for Protocol ST-96001 are provided in Attachment 3 as follows:
- Demographics
- Laboratory Data (BUN, Creatinine, Inorganic Phosphorus, Hematocrit)
- Carnitine Data for Analysis in Initial Supplement
- Carnitine Data Updated for Analysis Presented in Attachment 7

Printouts for Protocol ST-96002 are provided in Attachment 4 as follows:
- Demographics
- Laboratory Data (BUN, Creatinine, Inorganic Phosphorus, Hematocrit)
- Carnitine Data for Analysis in Initial Supplement
- Carnitine Data Updated for Analysis Presented in Attachment 7

Replacement Pages for P00835 Reanalysis

Replacement pages for the Protocol P00835 Reanalysis, which was provided in Volume 15 of the initial S-006 supplement of January 29, 1999, are provided as follows:
- Table 17.1 (Volume 15, page 000118) is provided in Attachment 5.
- Tables 12.1 - 12.4 (Volume 15, pages 000106 – 000109); and Appendices 13.1 - 13.3 (Volume 15, pages 000289 – 000291) are provided in Attachment 6.

These changes do not affect the SAS data sets used in the initial SNDA.

Table 17.1

We have detected an error in Table 17.1, page 000118, of NDA 20-182, Supplemental New Drug Application, January 29, 1999, Volume 15 of 29. Parameter estimates and p-values for the BUN outcome were incorrectly entered into this table. An accompanying replacement page contains the corrected values. The p-values that indicate the

significance of treatment and time effects have changed, but the new, corrected values have the same qualitative implications as the previous values. In particular, treatment and time effects remain highly significant, indicating that there is a significant difference between levocarnitine and placebo groups in BUN trends over time. Figure 3, page 000122 (Volume 15), which displays the observed and predicted BUN values over time, is unchanged.

A replacement Table 17.1 and the preceding discussion are provided in Attachment 5.

Tables 12.1 - 12.4 and Appendices 13.1 - 13.3

We have detected a programming error which affected the values of the test statistics and their degrees of freedom in Tables 12.1 - 12.4, pages 000106 - 000109, and Appendices 13.1 - 13.3, pages 000289 - 000291, of NDA 20-182, Supplemental New Drug Application, January 29, 1999, Volume 15 of 29. The accompanying replacement pages contain the corrected values. In the corrected tables some p-values have also changed because of the corrected degrees of freedom, but the p-values have changed by only one unit in the last significant digit. There are no qualitative changes in the implications of these p-values. For example, no p-value crosses the threshold of 0.05.

These tables all concern covariates that may predict one of the primary outcomes of the reanalysis. Examples are treatment group, gender and androgen use. The intent of the output is to identify covariates that might be used in subsequent regression models. It is these regression models and not Tables 12.1 - 12.4 and Appendices 13.1 - 13.3 that are the basis of our conclusions about the primary outcomes.

In preparing the tables for the NDA, we presented F-statistics with one numerator degree of freedom for two-group comparisons of means. The F-statistic is the square of the equivalent t-statistic but we labeled the F-value as a t-value. This error has now been corrected in the new tables. Additionally, there was an error in our criterion for using the Satterthwaite approximation to the variance of the heteroscedastic t-statistic. This has been corrected, slightly changing the degrees of freedom and so affecting the p-values as noted above. Again we point out that there were no qualitative or substantial quantitative implications of these errors.

Replacement Tables 12.1 - 12.4 and Appendices 13.1 - 13.3 as well as the preceding discussion are provided in Attachment 6.

Replacement pages for the analysis of ST-96001 carnitine blood level data and for the combined analysis of ST-96001/ST-96002 carnitine blood level data

These analyses were submitted in both Volume 6 (Item 6, Pharmacokinetics) and Volume 14 (Item 8/10 Clinical/Statistical) of the initial S-006 supplement of January 29, 1999. These replacement pages are necessitated by changes in individual data for four patients at one time point each as follows:

- Initial L-Carnitine, Total Carnitine, Acetyl-L-Carnitine, Ratio Acy/L-Carn for one patient in the 40 mg/kg levocarnitine group (Pt. 003).
- Week 24 Total Carnitine and Ratio Acy/L-Carn for two patients in the 40 mg/kg levocarnitine group (Pt. 015 and Pt. 146).
- Week 24 Acetyl-L-Carnitine for one patient in the placebo group (Pt. 145).

These changes were made due to data clarifications from the analysis laboratory. These changes were made to the SAS data set for carnitine data for Protocol ST-96001. In addition, the Screening Number was added to one patient in the 20 mg/kg levocarnitine group in Protocol ST-96002 (Pt. 613). The updated data sets for each protocol as well as the initial data sets are provided electronically.

The updates have resulted in slight changes to the tables that present carnitine results for Protocol ST-96001 and the combined protocols. There were no changes to the Protocol ST-96002 carnitine data that affected the submitted tables. The following tables in the SNDA have changed due to the modifications to the data for persons in Protocol ST-96001.

- Combined Protocol ST-96001 and Protocol ST-96002 (LCN4CAT BY VISITORD) (Initial SNDA, Vol. 6, Page 000008, and Vol. 14, Page 000006)
  One person moved from the cell for Initial - Less Than 20 mg L-Carnitine to the cell for Initial - 30 - < 40 mg L-Carnitine, resulting in changes to the percentages in the row for Less Than 20 mg L-Carnitine and in the row for 30 - < 40 mg L-Carnitine.

- Protocol ST-96001 Laboratory Test: L-Carnitine (Serum Free) (Initial SNDA, Vol. 6, Page 000009, and Vol. 14, Page 000007
  There are slight increases in the mean, median, and standard deviation for the Initial values of L-Carnitine for the L-Carnitine 40 mg treatment group.

- Protocol ST-96001 Laboratory Test: Total Carnitine (Initial SNDA, Vol. 6, Page 000010, and Vol. 14, Page 000008)
  There are slight increases in the mean and median and a slight decrease in the standard deviation for the Initial values of Total Carnitine for the L-Carnitine 40 mg treatment group. There are slight decreases in the mean and standard deviation for the Week 24 values of Total Carnitine for the L-Carnitine 40 mg treatment group.

- Protocol ST-96001 Laboratory Test: Acetyl-L-Carnitine (Initial SNDA, Vol. 6, Page 000011, and Vol. 14, Page 000009)
  There are slight increases in the mean and standard deviation for the Initial values of Acetyl-L-Carnitine for the L-Carnitine 40 mg treatment group. One person has an added value for Acetyl-L-Carnitine, resulting in an increase in the N from 29 to 30 and slight decreases in the mean, median, and standard deviation for the Week 24 values of Acetyl-L-Carnitine for the Placebo treatment group.

- Combined Protocol ST-96001 and Protocol ST-96002 Laboratory Test: L-Carnitine (Serum Free) (Initial SNDA, Vol. 6, Page 000015, and Vol. 14, Page 000013)
  There are slight increases in the mean, median, and standard deviation for the Initial values of L-Carnitine for the L-Carnitine 40 mg treatment group.

- Combined Protocol ST-96001 and Protocol ST-96002 Laboratory Test: Total Carnitine (Initial SNDA, Vol. 6, Page 000016, and Vol. 14, Page 000014)
  There are slight increases in the mean and median and a slight decrease in the standard deviation for the Initial values of Total Carnitine for the L-Carnitine 40 mg treatment group. There are slight decreases in the mean and standard deviation for the Week 24 values of Total Carnitine for the L-Carnitine 40 mg treatment group.

- Combined Protocol ST-96001 and Protocol ST-96002 Laboratory Test: Acetyl-L-Carnitine (Initial SNDA, Vol. 6, Page 000017, and Vol. 14, 000015)
  There are slight increases in the mean and standard deviation for the Initial values of Acetyl-L-Carnitine for the L-Carnitine 40 mg treatment group. One person has an added value for Acetyl-L-Carnitine, resulting in an increase in the N from 56 to 57 and slight decreases in the mean, median, and standard deviation for the Week 24 values of Acetyl-L-Carnitine for the Placebo treatment group.

The replacement pages provided in Attachment 7 contain the corrected values for these tables. In addition, we have included replacement pages for the Subject Data Listings for both protocols, since we have added footnotes to identify the imputed values and the one value of Week 12 Acetyl-L-Carnitine that was in the data but was set to missing for the analysis. The placement of the screening number and the pagination have changed slightly on these replacement listings. These Subject Data Listings replace the Subject Data Listings in Volume 6, Pages 000019-000048, and Volume 14, Pages 000017-000046 in the initial supplement. There were no qualitative or substantial quantitative implications of these data updates.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 948-1041.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

DESK COPY: Ms. Maureen Hess

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

June 10, 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

Four Month Safety Update

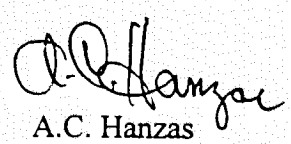
Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182. In addition, please refer to our January 29, 1999, supplement to NDA 20-182 (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.

Submitted herewith, in duplicate, is the four month safety update to this pending supplement. At this time there is no new safety information that has been learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling provided in S-006. There are no IND studies ongoing in this indication. No 15-day alert reports have been submitted.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 948-1041.

Sincerely,



A.C. Hanzas
Director, Regulatory Affairs

ACH/jmg

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

May 6, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocri
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 phone inquiry by Ms. Maureen Hess on May 5, 1999, regarding the need for a revised Environmental Assessment since the new indication will expand the use.

In response to this request we are claiming a categorical exclusion as provided for in CFR 25.31 (c). This exclusion is for substances that occur naturally in the environment and the requested action does not significantly alter the distribution in the environment. Levocarnitine is a naturally occurring substance and the expanded use in hemodialysis patients will not add significantly to the total environmental exposure. In addition, the use in this patient population is an Orphan Designation.

If you have any questions regarding this submission, do not hesitate to contact me at (301) 948-1041.

Sincerely,

A.C. Hanzas
Director, Regulatory Affairs

ACH/jmg

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SE1 006

January 29, 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

RE: NDA 20-182
Carnitor® (levocarnitine) Injection - Supplement for New Indication

Dear Dr. Sobel:

Please refer to our approved New Drug Application for Carnitor® (levocarnitine) Injection, NDA 20-182, and to a previously submitted NDA by Kendall McGaw Laboratories (NDA19-823) for the same product which was withdrawn without prejudice on June 27, 1991 (Attachment 1). Please also refer to your acknowledgement letter dated August 6, 1991 (Attachment 2). The withdrawn application provided for the treatment of the symptoms of levocarnitine deficiency in End Stage Renal Disease (ESRD) patients undergoing hemodialysis. We wish to reopen the file at this time and incorporate it by reference to this supplement. Please also refer to our Orphan Designation [redacted] for levocarnitine in the treatment of hemodialysis patients who exhibit symptoms associated with carnitine deficiency (Attachment 3). In addition, please refer to your correspondence of February 1, 1989, and October 20, 1989, regarding not approvability of the NDA and providing a description of deficiencies (Attachments 4 and 5).

Sigma-tau has acquired the ownership of NDA 19-823 filed by Kendall McGaw on January 27, 1988 (Attachment 6). At this time sigma-tau would like to reopen this file and incorporate it into this SNDA which will address the original issues and provide additional information regarding hemodialysis and levocarnitine.

The proposed indication would be for the treatment of manifestations of secondary carnitine deficiency in patients with End Stage Renal Disease who require hemodialysis. Sigma-tau intends to exercise orphan drug exclusivity following approval for this indication. As support for this revised labeling the following information is provided.

1. NDA 19-823 submitted January 27, 1988, which was not approvable based on certain deficiencies.

2. Response to the issues cited as deficiencies in the NDA 19-823 which have not been previously addressed (Attachment 9).

3. A reanalysis of the double blind placebo controlled study (Protocol P00835) submitted in NDA 19-823 to meet current standards and to review previous observations. This study was previously audited by FDA. The positive results by the FDA inspection by one investigator are included in Attachment 7.

4. A pharmacokinetic study in hemodialysis patients establishing a deficiency of levocarnitine (below normal level) and characterizing the plasma profile following repeat administration. Information regarding dose recommendations is provided from this study. In addition, plasma level results from two recently completed double blind placebo controlled studies are included.

5. An overview of the literature provided as a meta-analysis which provides a summary of the potential clinical benefits discussed in the literature. This review was conducted in France as part of the requirements for completing a medical degree.

6. A brief overview of the current use pattern of levocarnitine in patients on hemodialysis.

7. Draft statistical reports of the recent double blind studies conducted by sigma-tau to assess the effects of levocarnitine in hemodialysis patients on their exercise performance.

The data from the recently completed kinetic study, as well as the plasma levels from two recently completed double-blind, placebo-controlled studies, establish the reduction in carnitine levels in patients on hemodialysis and provide useful information for dosing. The reduction in carnitine levels and the resultant clinical complications are known from the metabolic deficiency states. A review by Pons and DeVivo describes the conditions associated with both primary and secondary carnitine deficiency syndromes. (See reference section for Item 3.) Hemodialysis is considered a secondary

carnitine deficiency syndrome. Levocarnitine is currently approved in the United Kingdom, Austria, Germany, Portugal, Spain, Switzerland, Turkey, Korea, Argentina and Venezuela for correcting this secondary carnitine deficiency in hemodialysis patients. The clinical symptoms that have been associated with primary carnitine deficiency can be expected to result from secondary deficiency states. The effects of replacement therapy with levocarnitine in secondary deficiencies, including therapy of hemodialysis patients, are self-evident. The correction and prevention of this deficiency are important especially when the disease (renal failure) has a high and predictable mortality. The effects on cardiac function associated with reduced carnitine levels are some of the most notable in such patients. The kinetic study supports the need for replacement therapy and demonstrates the positive result in correcting the deficiency.

In addition, the adequate and well-controlled study previously provided to FDA as well as the literature also suggest clinical effects that are consistent with an improved metabolic profile occurring with exogenous carnitine replacement.

Further support for the clinical benefit of levocarnitine in hemodialysis is the current status of clinical use in the dialysis community. In the U.S. the current sales of Carnitor Injection for hemodialysis are
This level suggests a decision

In addition, the Medicare division supporting the ESRD program has reached a positive conclusion regarding the need for levocarnitine replacement therapy. A copy of their newsletter describing guidelines for use is included (Attachment 8). However, the absence of a definitive statement in the labeling has led to reimbursement difficulties for some patients in some states.

Based on the results of the pharmacokinetic studies, previous clinical trials, literature overview, current medical practice, and an apparent need to equalize reimbursement issues, sigma-tau proposes to revise the labeling indication section as follows:

The recommended dose is 20 mg/kg dry body weight as a slow 2–3 minute bolus injection into the venous return line after each dialysis session. It is recommended that therapy begin after the patient has been on hemodialysis for a period of six months. Post-dialysis levocarnitine plasma levels approach physiological levels after approximately two months of therapy at 20 mg/kg. After two months of therapy and based on clinical assessment, the dose may be adjusted to 5 mg/kg after each dialysis session.

The 1989 deficiency letter for NDA 19-823 questioned the clinical relevance of replacement therapy and the clinical benefit resulting from replacement therapy. A period of growing use by clinicians helps provide support to earlier observations that are suggestive of a clinical need and benefit for replacing levocarnitine lost in hemodialysis.

If you have any questions regarding this submission, please call me at (301) 948-1041.

Sincerely yours,

A.C. Hanzas
Director, Regulatory Affairs