

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER for: 020182, S006**

**ADMINISTRATIVE DOCUMENTS and  
CORRESPONDENCE**

PATENT INFORMATION

There are no patents claiming the new drug substance or for use of levocarnitine injection in the treatment of manifestations of carnitine deficiency in patients with ESRD who require dialysis.

EXCLUSIVITY

Pursuant to Section 526 of the FDCA, Carnitor® levocarnitine was granted orphan drug designation for the treatment of manifestations of carnitine deficiency in patients with ESRD who require dialysis. See FDA letter dated September 6, 1988 under Item 3: Attachments.

We have notified the Office of Orphan Products Development of our intention to exercise the statutory period of seven (7) years of orphan drug exclusivity if we are the first sponsor to obtain market approval for Carnitor® injection for the treatment of the above orphan drug designation indication.

APPEARS THIS WAY  
ON ORIGINAL

### Exclusivity Checklist

|   |                  |    |                                     |
|---|------------------|----|-------------------------------------|
| NDA: <u>21-082-20-182</u>   |                  |    |                                     |
| Trade Name: <u>Carnitor</u>   |                  |    |                                     |
| Generic Name: <u>Levocarnitine Injection</u>  |                  |    |                                     |
| Applicant Name: <u>Sigma-Tau Pharmaceuticals</u>  |                  |    |                                     |
| Division: <u>HFD-510</u>  |                  |    |                                     |
| Project Manager: <u>Maureen Hess</u>  |                  |    |                                     |
| Approval Date:  |                  |    |                                     |
| <b>PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?</b>  |                  |    |                                     |
| 1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.  |                  |    |                                     |
| a. Is it an original NDA?   | Yes              | No | <input checked="" type="checkbox"/> |
| b. Is it an effectiveness supplement?   | Yes              | No | <input checked="" type="checkbox"/> |
| c. If yes, what type? (SE1, SE2, etc.)  | <u>SE1</u>       |    |                                     |
| Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")   | Yes              | No | <input checked="" type="checkbox"/> |
| If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. |                  |    |                                     |
| Explanation:  |                  |    |                                     |
| If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:   |                  |    |                                     |
| Explanation:  |                  |    |                                     |
| d. Did the applicant request exclusivity?   | Yes              | No | <input checked="" type="checkbox"/> |
| If the answer to (d) is "yes," how many years of exclusivity did the applicant request?   | <u>Seven (7)</u> |    |                                     |
| <b>IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.</b>  |                  |    |                                     |
| 2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?  | Yes              | No | <input checked="" type="checkbox"/> |
| If yes, NDA #   |                  |    |                                     |
| Drug Name:  |                  |    |                                     |

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.**

3. Is this drug product or indication a DESI upgrade?  Yes  No  X

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

N/A

1. Single active ingredient product.  Yes  No

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

|     |    |
|-----|----|
| Yes | No |
| Yes | No |

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

|              |  |
|--------------|--|
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |

2. Combination product.  Yes  No

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

|     |    |
|-----|----|
| Yes | No |
| Yes | No |

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

|              |  |
|--------------|--|
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |

NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

|   |     |   |    |  |
|---|-----|---|----|--|
| <p>1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.</p> | Yes | X | No |  |
|---|-----|---|----|--|

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

|   |     |   |    |  |
|---|-----|---|----|--|
| <p>a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?</p> | Yes | X | No |  |
|---|-----|---|----|--|

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

|  |     |  |    |   |
|--|-----|--|----|---|
| <p>b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?</p> | Yes |  | No | X |
|--|-----|--|----|---|

|   |     |  |    |  |
|---|-----|--|----|--|
| <p>1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.</p> | Yes |  | No |  |
|---|-----|--|----|--|

If yes, explain:

|   |     |  |    |   |
|---|-----|--|----|---|
| 2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? | Yes |  | No | X |
|---|-----|--|----|---|

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

|  |  |
|--|--|
| Investigation #1, Study #: ST-198-US-96-PK01 |  |
| Investigation #2, Study #: ST-96001          |  |
| Investigation #3, Study #: ST-96002          |  |

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

|                  |     |  |    |   |
|------------------|-----|--|----|---|
| Investigation #1 | Yes |  | No | X |
| Investigation #2 | Yes |  | No | X |
| Investigation #3 | Yes |  | No | X |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

|                                |  |
|--------------------------------|--|
| Investigation #1 -- NDA Number |  |
| Investigation #2 -- NDA Number |  |
| Investigation #3 -- NDA Number |  |

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

|                  |     |  |    |   |
|------------------|-----|--|----|---|
| Investigation #1 | Yes |  | No | X |
| Investigation #2 | Yes |  | No | X |
| Investigation #3 | Yes |  | No | X |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

|                                |  |
|--------------------------------|--|
| Investigation #1 -- NDA Number |  |
| Investigation #2 -- NDA Number |  |
| Investigation #3 -- NDA Number |  |

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the

application or supplement that is essential to the approval (i.e., the investigations listed in #2 (c), less any that are not "new"):

|                  |                   |
|------------------|-------------------|
| Investigation #1 | ST-198-US-96-PK01 |
| Investigation #2 | ST-96001          |
| Investigation #3 | ST-96002          |

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

|                  |                 |     |                                     |    |                          |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|
| Investigation #1 | IND# [redacted] | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|

Explain:

|                  |                 |     |                                     |    |                          |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|
| Investigation #2 | IND# [redacted] | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|

Explain:

|                  |                 |     |                                     |    |                          |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|
| Investigation #3 | IND# [redacted] | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-----------------|-----|-------------------------------------|----|--------------------------|

Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

|                  |       |     |                          |    |                          |
|------------------|-------|-----|--------------------------|----|--------------------------|
| Investigation #1 | IND#: | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-------|-----|--------------------------|----|--------------------------|

Explain:

|                  |       |     |                          |    |                          |
|------------------|-------|-----|--------------------------|----|--------------------------|
| Investigation #2 | IND#: | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-------|-----|--------------------------|----|--------------------------|

Explain:

|                  |       |     |                          |    |                          |
|------------------|-------|-----|--------------------------|----|--------------------------|
| Investigation #3 | IND#: | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
|------------------|-------|-----|--------------------------|----|--------------------------|

Explain:

|   |     |  |    |   |
|---|-----|--|----|---|
| <p>c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)</p> | Yes |  | No | X |
| <p>If yes, explain:</p>   |     |  |    |   |



Signature of PM/CSO           /S/            
 Date: December 10, 1999

Signature of Division Director           /S/            
 Date: 12-14-99

cc:  
 Original NDA  
 Division File  
 HFD-93 Mary Ann Holovac



### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

|                           |              |                             |   |
|---------------------------|--------------|-----------------------------|---|
| <b>NDA/BLA Number:</b>    | <u>20182</u> | <b>Trade Name:</b>          | <u>CARNITOR (LEVOCARNITINE) INJ</u>   |
| <b>Supplement Number:</b> | <u>6</u>     | <b>Generic Name:</b>        | <u>LEVOCARNITINE</u>  |
| <b>Supplement Type:</b>   | <u>SE1</u>   | <b>Dosage Form:</b>         | <u>Injection</u>  |
| <b>Regulatory Action:</b> | <u>PN</u>    | <b>Proposed Indication:</b> | <u>Prevention and treatment of carnitine deficiency in patients with end stage renal disease who are undergoing dialysis.</u> |

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, Pediatric content not necessary because of ~~pediatric waiver~~ orphan designation

**What are the INTENDED Pediatric Age Groups for this submission?**

NeoNates (0-30 Days )     Children (25 Months-12 years)  
 Infants (1-24 Months)     Adolescents (13-16 Years)

**Label Adequacy**            Does Not Apply  
**Formulation Status**        \_\_\_\_\_  
**Studies Needed**            \_\_\_\_\_  
**Study Status**                \_\_\_\_\_

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

**COMMENTS:**

Indication is a designated orphan (12/13/99)

Orphan Product

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN HESS

  
 \_\_\_\_\_  
 Signature

12/13/99  
 \_\_\_\_\_  
 Date

DEBARMENT CERTIFICATION STATEMENT

January 29, 1999

sigma-tau Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this Application.

*A. C. Hanzas*

AC Hanzas  
Director, Regulatory Affairs

ACH/ebs

APPEARS THIS WAY  
ON ORIGINAL

**NDA 20-182/S-006**

**Carnitor (Levocarnitine) injection**

**Sigma Tau (Gaithersburg, MD)**

**Date of submission: January 29, 1999**

**SE-1: New indication for the treatment of carnitine deficiency in patients with end-stage renal disease (ESRD) on dialysis**

**December 13, 1999: Memo to the action package regarding lack of need for inspections by DSI**

No inspections by the Division of Scientific Investigations (DSI) were requested for this sNDA. The clinical trials were, in effect, pharmacokinetic/pharmacodynamic studies with biochemical endpoints. Adequate numbers of patients were exposed for purposes of safety assessment (approximately 150 patients total). There was no assessment of effects on clinical outcomes, per se. Because of the small size of the patient database, the orphan status of the drug for this indication, and the necessary expertise among the physicians and nurses caring for dialysis patients, DSI was not asked to conduct any inspections.

/S/ 12-13-99

CC: NDA 20-182/S-006  
HFD-510 / Div File



**sigma-tau**  
PHARMACEUTICALS, Inc.

800 south frederick avenue  
gaithersburg, md 20877

**NDA SUPP AMEND**  
**SCP-006-SU**

telephone: (301) 948-1041

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

**ORIGINAL**

**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



*Handwritten:* NDA  
ISI  
12-13-99

**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.

|                                 |   |
|---------------------------------|---|
| REVIEWS COMPLETED               |   |
| CSO ACTION:                     |   |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS                    | DATE  |

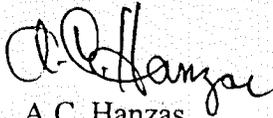
**000001**

NDA 20-182

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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

APPEARS THIS WAY  
ON ORIGINAL

000002

## MEMORANDUM OF TELECON

DATE: May 4, 1999

APPLICATION NUMBER: NDA 20-182/S-006; Carnitor (levocarnitine) Injection

BETWEEN:

Name: A.C. Hanzas

Phone: (301) 948-1041

Representing: Sigma-tau Pharmaceuticals

AND

Name: Maureen Hess, MPH, RD

Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Environmental Assessment

Phone call to Sigma-tau to inform them that it will be necessary to either update their environmental assessment or claim categorical exclusion. CSO referred the sponsor to CFR 25.31 for the class of actions that are categorically excluded and, therefore, would not require an updated EA. CSO informed the sponsor that either an updated EA or claim of categorical exclusion should be submitted to the supplement.

/S/

Maureen Hess  
Consumer Safety Officer

cc: Original NDA 20-182/S-006  
HFD-510/Div. File  
HFD-510/Maureen Hess  
HFD-510/SMarkofsky/DWu/MHess

APPEARS THIS WAY  
ON ORIGINAL

TELECON

FEB 3 1999

Sigma Tau  
800 South Frederick Ave.  
Suite 300-  
Gaithersburg, MD 20877

Attention: Mr. A. C. Hanzas  
Director, Regulatory Affairs

Dear Mr. Hanzas:

We acknowledge receipt of your supplemental application for the following:

|                     |                                     |
|---------------------|-------------------------------------|
| Name of Drug:       | Carnitor® (Levocarnitine) Injection |
| NDA Number:         | 20-182                              |
| Supplement Number:  | S- 006                              |
| Date of Supplement: | January 29, 1999                    |
| Date of Receipt:    | February 01, 1999                   |

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 2, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Office of Drug Evaluation II  
Attention: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely

A rectangular box containing the handwritten initials "/S/".

Eric Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine  
Drug Products, HFD-510  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research