

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-881

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-881

FIRM: GensiaSicor Pharmaceutical (GSP)
19 Hughes
Irvine, CA 92618

DOSAGE FORM: Injectable

STRENGTH: 200 mg/mL

DRUG: Levocarnitine Injection USP

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities is acceptable on 1-8-01.

BIO STUDY:
Bio status: Acceptable as of 7-26-00.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV is not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Acceptable for approval per A. Payne's review completed on 1-19-01.

STERILIZATION VALIDATION (IF APPLICABLE):
Micro review: Acceptable per N. Nath review completed on 2-22-01.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):
No bio batch. Bio waiver is requested and granted.

Source of NDS:
DM
th. 5-01 by

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Stability batches are:

Lot # X99E206 (Size: for 500 mg/vial.

Lot # X99E106 (Size: for 1 g/vial.

Lot # X99E106F (Size:) for 2.5 g/vial.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Intended production batch size: (for 500 mg/Vial).

Intended production batch size: (for 1 g and 2.5 g/vial)

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

Mujahid L. Shaikh/3/7/01
Review Chemist
Division of Chemistry I
OGD/CDER

Mujahid Shaikh 3/13/01

BR & M Shaikh 3/13/01

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #1

January 12, 2001

A. 1. ANDA 75-881

APPLICANT : Gensia Sicor Pharmaceuticals, Inc.

2. PRODUCT NAME: Levocarnitine Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 200 mg/mL;
2.5 mL (500 mg) in 3.5 mL vials, 5 mL (1 g) in 6 mL
vials and 12.5 mL (2.5 g) in 20 mL vials; Intravenous

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Treatment of carnitine
deficiency.

B. 1. DATE OF INITIAL SUBMISSION: May 19, 2000

Subject of this Review (Recd. May 23, 2000)

2. DATE OF AMENDMENTS: July 14, 2000 (New Correspondence)
Subject of this Review (Recd. July 17, 2000)

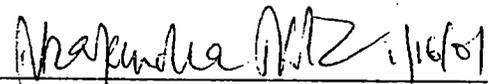
3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: January 8, 2001

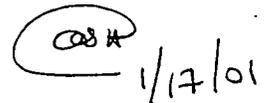
C. REMARKS: The subject drug product is manufactured by
Gensia-Sicor in its Irvine, CA facility and is filled in
3.5, 6 and 20-mL single dose glass vials on the Filling
Lines #1 and #2.

The present review includes filtration validation
submitted as part of the new correspondence, dated July 14,
2000.

D. CONCLUSIONS: The submission is not recommended for approval
on the basis of sterility assurance. Specific comments are
provided in "E. Review Notes" and "Microbiology Comments to
be Provided to the Applicant" found at the end of this
review. The deficiencies represent a Fax amendment.



Nrapendra Nath, Ph. D.



cc:

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-881

Date of Submission: May 19, 2000

Applicant's Name: Gensia Sicor

Established Name: Levocarnitine Injection USP, 200 mg/mL

Labeling Deficiencies:

1. CONTAINER (2.5 mL, 5 mL and 12.5 mL)
 - a. On your label provided as part of the side by side comparison for the 500 mg/2.5 mL package size, the following appears "3 mL Single Dose Vial", however the rest of the labels for this package size read, "Single Dose Vial". We request that "3 mL" does not appear on your final print labels.
 - b. Revise your container labels so that "USP" appears immediately following the established name; i.e. "Levocarnitine Injection, USP".
2. CARTON (5 x 2.5 mL, 5 x 5 mL and 5 x 12.5 mL)
 - a. Submit carton labeling for the 5 x 5 mL and the 5 x 12.5 mL package sizes for review and comment.
 - b. Revise your carton labels so that "USP" appears immediately following the established name; i.e. "Levocarnitine Injection, USP".
3. SHELF PACK LABEL
 - a. Revise your shelf pack labels to read "5 x 2.5 mL", "5 x 5 mL", and "5 x 12.5 mL" rather than "5 x 3.5 mL", "5 x 6 mL" and "5 x 20 mL".
 - b. Revise your shelf pack labels so that "USP" appears immediately following the established name; i.e. "Levocarnitine Injection, USP".
4. INSERT
 - a. TITLE - Revise your insert so that "USP" appears immediately following the established name; i.e. "Levocarnitine Injection, USP".
 - b. DESCRIPTION- Revise the second paragraph of this section to read as follows:

The chemical name of levocarnitine is 3-carboxy-2(R)-hydroxy-N, N, N-trimethyl-1-propanaminium, inner salt. Levocarnitine is a white crystalline, hygroscopic powder. It is readily soluble in water, hot alcohol, and insoluble in acetone. The specific rotation of levocarnitine is between -29° and -32°. Its chemical structure is:
 - c. CLINICAL PHARMACOLOGY
 - i. Revise the fourth sentence of the first paragraph of this section to read as follows:

In skeletal and cardiac muscle, fatty acids are the main substrate for energy production.
 - ii. Revise the fifth sentence of the first paragraph of this section to read as follows:

Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, RBC, and/or tissues.
 - iii. Second paragraph, first sentence - Revise to read as follows:

Secondary carnitine deficiency can be a consequence of inborn errors of metabolism or iatrogenic factors such as hemodialysis.
 - iv. Second paragraph, seventh sentence - Revise "Levocarnitine deficiency" to read "Carnitine deficiency" and revise "urine levels" to read "urine concentrations.
 - v. Second paragraph, eighth sentence - Revise to read as follows:

Further, this condition may be associated with a plasma concentration ratio of

acylcarnitine/levocarnitine greater than 0.4 or abnormally elevated concentrations of acylcarnitine in the urine.

- vi. Second paragraph; last sentence – Revise “plasma free levocarnitine” to read “plasma levocarnitine”.

d. **BIOAVAILABILITY/PHARMACOKINETICS**

- i. Revise this section heading to read “PHARMACOKINETICS”.
ii. Beginning with the second sentence, revise this section as follows:

Following 4 days of dosing with 6 tablets of levocarnitine 330 mg bid or 2 grams of levocarnitine oral solution bid, the maximum plasma concentration (C_{max}) was about 80 $\mu\text{mol/L}$ and the time to maximum plasma concentration (T_{max}) occurred at 3.3 hours.

The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg/kg of levocarnitine were described by a two-compartment model. Following a single IV administration, approximately 76% of the levocarnitine dose was excreted in the urine during the 0-24 hour interval. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half-life was 0.585 hours and the mean apparent terminal elimination half-life was 17.4 hours.

The absolute bioavailability of levocarnitine from the two oral formulations of levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was $15.1 \pm 5.3\%$ for levocarnitine tablets and $15.9 \pm 4.9\%$ for levocarnitine oral solution.

Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h.

Levocarnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.⁹

e. **METABOLISM AND EXCRETION**

- i. Revise the first sentence of this section to read as follows:

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [³H-methyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days.

- ii. Revise the last two sentences of the first paragraph of this section to read as follows:

Urinary excretion of levocarnitine was about 4 to 8% of the dose. Fecal excretion of total carnitine was less than 1% of the administered dose.¹⁰

- iii. Revise the second paragraph to read as follows:

After attainment of steady state following 4 days of oral administration of levocarnitine tablets (1980 mg q 12 h) or Oral Solution (2000 mg q 12 h) to 15 healthy male volunteers, the mean urinary excretion of levocarnitine during single dosing interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

f. **PRECAUTIONS (Nursing Mothers)** – Revise to read as follows:

Levocarnitine supplementation in nursing mothers has not been specifically studied.

Studies in dairy cows indicate that the concentration of levocarnitine in milk is increased following exogenous administrations of levocarnitine. In nursing mothers receiving levocarnitine, any risks

to the child of excess carnitine intake need to be weighed against the benefits of levocarnitine supplementation to the mother. Consideration may be given to discontinuation of nursing or of levocarnitine treatment.

g. **OVERDOSAGE**

i. Include the following to appear as the second sentence:

Levocarnitine is easily removed from plasma by dialysis.

ii. Revise the second sentence to read as follows:

The intravenous LD₅₀ of levocarnitine in rats is 5.4 g/kg and the oral LD₅₀ of levocarnitine in mice is 19.2 g/kg.

h. **DOSAGE AND ADMINISTRATION**

i. Begin a new paragraph with the second sentence of this section and include the following sub-section heading:

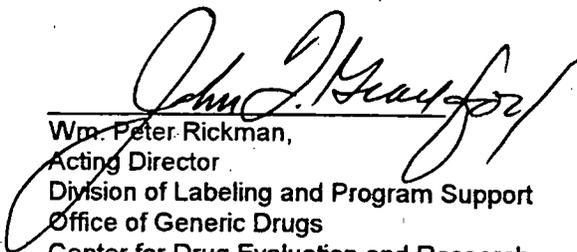
Metabolic Disorders

The recommended dose...

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Wm. Peter Rickman,
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-881

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia O. Gustavson
19 Hughes
Irvine, CA 92618-1902
|||||

JUL 20 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated June 29, 2000 and your correspondence dated July 14, 2000.

NAME OF DRUG: Levocarnitine Injection USP, 200 mg/mL, 2.5 mL, 5 mL and 12.5 mL vials

DATE OF APPLICATION: May 19, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 23, 2000

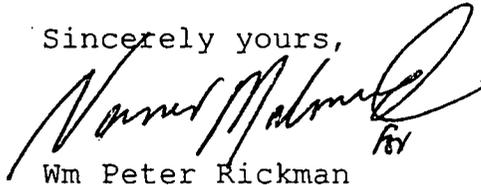
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research