

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-881

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.3

2. ANDA # 75-881

3. NAME AND ADDRESS OF APPLICANT

GensiaSicor Pharmaceuticals Inc. (GSP)
19 Hughes
Irvine, CA 92618

4. BASIS OF SUBMISSION

The listed drug product is Carnitor® (Levocarnitine Injection USP), 200 mg/mL vial manufactured by Sigma-Tau Pharmaceuticals.

There are no patents that claim the listed drug referred to in this application.

Market exclusivity are granted for Carnitor which expires on December 15, 2002, and December 15, 2006.

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product marketed by Sigma-Tau Pharmaceuticals.

The proposed 2.5 g/12.5 mL product differs from the listed drug product only in the total drug content. The Agency has approved their petition for this strength under Section 505(j)(2)(C (i) of the Act.

GensiaSicor will market Levocarnitine Injection as 500 mg/2.5 mL, 1g/5 mL and 2.5 g/12.5 mL.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used

7. NONPROPRIETARY NAME

Levocarnitine Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 5-19-00

NC: 7-14-00

Minor Amendment: 12-22-00 (Response to 11-24 NA letter)

Amendment (Response to micro deficiencies): 1-19-01

* Minor Amendment: 2-14-01

FDA:

Accepted for filing: 5-23-00 (Acknowledgment letter: 7-20-00)

NA letter: 11-24-00

Micro deficiency letter: 1-19-01

NA letter: 2-6-01

10. PHARMACOLOGICAL CATEGORY

To treat inborn metabolism error that results in Carnitine deficiency

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Injection

14. POTENCY

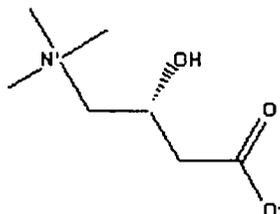
200 mg/ml

[500 mg/2.5 mL, 1 g/5 mL & 2.5 g/12.5 mL]

15. CHEMICAL NAME AND STRUCTURE

Name: R-3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium Hydroxide, inner salt

M.W: 161.20



16. RECORDS AND REPORTS
N/A

17. COMMENTS

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18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
3-7-01

cc:

e

Endorsements:

... and make 3/13/01

- for mSinde 3/13/01

Page (s)

2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chem Rev 3

3/7/01

FEB 06 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-881

APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Levocarnitine Injection USP, 200 mg/mL

The deficiencies presented below represent MINOR deficiencies.

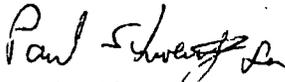
A. Deficiencies:

1. DMF ~~is inadequate~~ is inadequate.
Please ensure a response to the recent FDA letter.
2. Your calculation of the Upper Limit found in the table on page 10 of your recent amendment appears in error. Please clarify or correct.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Microbiological review for your amendment dated January 19, 2001 is pending.

Sincerely yours,



Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

NOV 24 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-881

APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Levocarnitine Injection USP, 200 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF is inadequate. Please ensure a response to the recent FDA letter.
2. Please provide a complete blank manufacturing batch record for the intended production size batch of s including information regarding the split fill into 5 mL and 12.5 mL vials.
3. Please revise your release and stability specifications to include the test and limit for color expressed in APHA color units. Alternatively, you may establish a correlation between your units (Hunter color units) and APHA color units.
4. Please revise your drug product release specifications to state "Meets the requirements of USP <1> Injections".
5. Please revise your post-approval stability protocol to include stability monitoring for vials stored in the upright position for all studies. This testing may be done at the annual test stations.
6. On page 200248, you mentioned that you will evaluate stability on first three commercial lots of the smallest and largest fill size for each container/closure system. Please revise your testing schedule to include all three fill sizes of the drug product.
7. The target overfill for the 12.5 mL vial appears excessive. Please revise or justify.
8. Please clarify the "OOSR" and "DEV" notations included on your stability reports and explain the significance in relation to the submitted data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.
2. Labeling deficiencies will also need to be addressed in your reply.
3. Microbiological review for the sterilization process is pending.
4. Please provide any additional stability data that is available for the exhibit batches.
5. Please note that future accelerated stability studies for parenteral liquids should include complete testing for both orientations at all test stations.

Sincerely yours,



2 Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research