CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-567

ADMINISTRATIVE DOCUMENTS

ANDA NUMBER 75-567

FIRM: Bedford Laboratories

DOSAGE FORM: Injection

STRENGTH: 200 mg/ml

DRUG: Levocarnitine

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable April 12, 2000.

BIO STUDY: A waiver of the *in-vivo* bioequivalence study requirement for the drug product was granted per the Division of Bioequivalence 3/11/99.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

N/A

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

2.5 ml fill:

:wson

ıg

stopper.

inum Seal.

5.0 ml fill:

Seal.

Data are provided for exhibit lots 0917-86-37734B (2.5-mL container) and 0917-44-37733B (5.0-mL container).

3-month data for samples stored upright and inverted at 40° C/75% RH and tested at 0, 1, 2 and 3-months.

24-month data for samples stored upright and inverted at 25° C ± 2° C/60% RH ± 5% RH and tested at 0, 3, 6, 9, 12, 18 and 24-months.

LABELING: Satisfactory per the January 9, 2001, 2001 review.

STERILIZATION VALIDATION (IF APPLICABLE):

Recommended for approval on the basis of sterility assurance per the October 18, 2000 Microbiology review.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): (Yes.

Exhibit lots 0917-86-37734B (2.5-mL container) and 0917-44-37733B (5.0-mL container) (total for 2.5 ml fill and 5.0 ml fill)

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):

Same Process

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

Same Process

(total for 2.5 ml fill and 5.0 ml fill)

Review Chemist: Shirley S. Brown Shirley S Brown 3/20/01
Team Leader: Michael Smela DC for M Smela 3/21/01
Date: March 12, 2001

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

ANDA Number: 75-567 **Date of Submission: October 6, 2000**
Applicant's Name: Bedford Laboratories
Established Name: Levocarnitine Injection USP, 200 mg/mL, 2.5 mL and 5 mL vials
Labeling Deficiencies:

1. GENERAL COMMENTS – Please update your patent/exclusivity statements.
2. CONTAINER (2.5 mL and 5 mL vial) – Satisfactory in printer's proof as of October 6, 2000 submission.
3. CARTON (10 x 2.5 mL and 10 x 5 mL) – Satisfactory in printer's proof as of October 6, 2000 submission.
4. INSERT – Due to changes in the insert labeling for the reference listed drug, CARNITOR® (Sigma-Tau; NDA 20-182/S-006; approved December 15, 1999), revise your insert as follows:

Please note that CARNITOR® has received Orphan Drug Exclusivity for "Treatment of manifestations of carnitine deficiency in patients with end stage renal disease who require dialysis" until December 15, 2006.

a. CLINICAL PHARMACOLOGY
   i. (First paragraph, second sentence)- Revise "therefore" to read "thereby".
   ii. (First paragraph, fourth sentence) – Revise to read as follows:

   In skeletal and cardiac muscle, fatty acids are the main substrate for energy production.

   iii. (First paragraph, fifth sentence)- Begin a new paragraph and revise as follows:

   Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, RBC, and/or tissues.

   iv. (Second paragraph, first sentence) – Revise to read as follows:

   ...errors of metabolism or iatrogenic factors such as hemodialysis.

   v. (Second paragraph, 7^{th} & 8^{th} sentences) – Revise to read as follows:

   ...and/or urine concentrations. 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. (Bioavailability/Pharmacokinetics) – Delete "Bioavailability" from this subsection heading.
   vii. (Bioavailability/Pharmacokinetics) – Revise this subsection to read as follows:

   ...Oral Solution. Following 4 days of dosing with 6 tablets of levocarnitine 330 mg bid or 2 g of levocarnitine oral solution bid, the maximum plasma concentration (C_{max}) was about 80 micromole/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 i.v. administration, approximately 76% of the levocarnitine dose was excreted in urine during the 0-24h 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 ± 5.3% for levocarnitine tablets and 15.9 ± 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]

viii. (Metabolism and Excretion) – Revise the first sentence in paragraph one to read as follows:

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [^{3}H-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.

ix. (Metabolism and Excretion) – first paragraph, 4th & 5th sentences- Revise 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]

x. (Metabolism and Excretion) – 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 12h) or oral solution (2000 mg q 12h) to 15 healthy male volunteers, the mean urinary excretion of levocarnitine during a single dose interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

b. PRECAUTIONS(Nursing Mothers) – Revise this subsection 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 administration 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.

c. OVERDOSAGE – Revise the second sentence in this section to read as follows:

Levocarnitine is easily removed from plasma by dialysis. The intravenous LD_{50} of levocarnitine in rats is 5.4 g/kg and the oral LD_{50} of levocarnitine in mice is 19.2 g/kg.

d. OVERDOSAGE- Beginning with the second sentence of the first paragraph, start a new subsection and title it "Metabolic Disorders".

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

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

ANDA Number: 75-567 **Date of Submission: September 10, 1999**
Applicant's Name: Bedford Laboratories
Established Name: Levocarnitine Injection USP, 200 mg/mL, 2.5 mL and 5 mL vials

Labeling Deficiencies:

1. CONTAINER (2.5 mL and 5 mL vial)

   a. Revise the "Each vial..." statement to read as follows:

      Each mL contains Levocarnitine 200 mg,...

   b. 2.5 mL only - Enhance the prominence and conspicuousness of the established name and strength. If space is a concern, you may delete some statements. We refer you to 21 CFR 201.10(i) for guidance.

   c. Delete "See USP." from your storage statement.

2. CARTON (5 x 2.5 mL and 5 x 5 mL)

   a. See comment (a) under container.

   b. See comment (c) under container.

4. INSERT

   a. PRECAUTIONS (Teratogenic Effects – Pregnancy Category B)

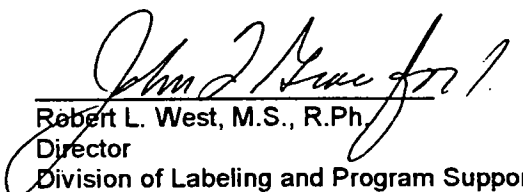
      Delete the second paragraph, which begins "Seizures have been..."

   b. See comment (c) under container.

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



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 75-567 **Date of Submission: January 12, 1999**

Applicant's Name: Bedford Laboratories

Established Name: Levocarnitine Injection USP, 200 mg/mL, 2.5 mL and 5 mL vials

Labeling Deficiencies:

1. GENERAL COMMENTS:

   We encourage you to use "USP" in conjunction with the established name.

2. CONTAINER (2.5 mL and 5 mL vial)

   a. See comment under GENERAL COMMENTS.

   b. Revise your storage recommendation to read as follows:

      Store vials at room temperature (25°C). See USP. Retain vial in carton until time of use. Protect from light. Discard unused portion of an opened vial, as they contain no preservative.

3. CARTON (5 x 2.5 mL and 5 x 5 mL)

   a. See comment under GENERAL COMMENTS.

   b. Revise your storage recommendation to read as follows:

      Store vials at room temperature 25°C (77°F). See USP. Retain vial in carton until time of use. Protect from light. Discard unused portion of an opened vial, as they contain no preservative.

4. INSERT

a. TITLE

i. We encourage the inclusion of "Rx only" in this section.

ii. See GENERAL COMMENTS.

b. DESCRIPTION

i. Revise "chemical structure" to read "structural formula".

c. CLINICAL PHARMACOLOGY

i. Revise the third sentence of paragraph two of this section to read as follows:

…are: glutaric aciduria II,…

ii. Revise the seventh sentence of paragraph two of this section to read as follows:

…20 micromole/L at one week post term…

d. PRECAUTIONS

i. Pregnancy: Teratongenic Effects- Pregnancy Category B.

Revise "Teratongenic" to read "Teratogenic" in this subsection title.

e. ADVERSE REACTIONS

i. Include the following to appear as the second paragraph of this section:

Seizures have been reported to occur in patients with or without pre-existing seizure activity receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, and increase in seizure frequency and/or severity has been reported.

f. HOW SUPPLIED

i. Revise your storage recommendation to read as follows:

Store vials at room temperature 25°C (77°F). See USP. Retain vial…

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

John D. Grace for/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: #75-567 APPLICANT: Bedford Pharmaceuticals, Inc.

DRUG PRODUCT: Levocarnitine Injection 200 mg/mL
2.5 & 5-mL; Single-Use Vials

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research