Center for Drug Evaluation and Research

Approval Package for:

Application Number: 018948/S016

Trade Name: CARNITOR TABLETS

Generic Name: LEVOCARNITINE

Sponsor: SIGMA-TAU PHARMACEUTICALS, INC.

Approval Date: 07/14/92
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018948/S016

APPROVAL LETTER
Sigma-Tau Pharmaceuticals, Inc.
Attention: Edward D. Helton, Ph.D.
Director, Research and Regulatory Affairs
200 Orchard Ridge Drive
Gaithersburg, MD 20878

Dear Dr. Helton:

Reference is made to your supplemental new drug application dated June 30, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carnitor (levocarnitine) Tablets.

The supplement provides for

We have completed our review of this supplemental application, along with final printed labeling, and it is approved, effective on the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

[Signature]

Solomón Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch.
HFD-510
HFC-130/JAllen
HFD-80/labelling attached
HFD-500/LRipper/labelling attached
HFD-638/labelling attached
HFD-735/labelling attached
HFD-510/DWu/YYChiu
HFD-511/LBraithwaite for SDinstead/07.13.92/N18948AP.S16/ft/nls/7/13/92
Concurrence: DWu, YYChiu, 7.13.92

SUPPLEMENT APPROVAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

FINAL PRINTED LABELING
CARNITOR® (Levcarnitine) Tablets (330 mg) CARNITOR® (Levcarnitine) Oral Solution (1 g per 10 mL multidose)

For oral use only. Not for parenteral use.

Description
Levcarnitine is a 1-l-beta-hydroxy-gamma-aminobutyric butyric acid (sera salt). As a bulk drug substance it is a white powder with a melting point of 198-202°C and is readily soluble in water. The Levcarnitine is the biologically active form. Its chemical structure is:

Each CARNITOR® (Levcarnitine) Tablet contains 330 mg of levcarnitine and the inactive ingredients magnesium stearate, microcrystalline cellulose, calcium silicate and phenylalanine.

Each 118 mL container of the CARNITOR® (Levcarnitine) Oral Solution contains 1 g of levcarnitine/10 mL, sorbic acid, DL-malic acid, red coloring and artificial flavor. Methyl paraben NF and Propylparaben NF are added as preservatives. The pH is approximately 5.

Clinical pharmacology
Levcarnitine is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, therefore delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle they serve as major fuel. Primary systemic carnitine deficiency is characterized by low plasma, RBC, and tissue levels. The resulting impairment in fatty acid metabolism manifests itself as elevated lactate and free fatty acids, diminished heterogeneity, and lipoid infiltration of liver and muscle. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that biocumulate such as medium chain acyl-CoA esters.

Bioavailability
The absolute bioavailability of CARNITOR® (Levcarnitine) Tablets and the Oral Solution, have not been determined in well controlled studies.

Metabolism and excretion
The majority of body carnitine is excreted in the urine and feces. In renal failure, carnitine levels may rise.

Indications and usage
CARNITOR® (Levcarnitine) is indicated in the treatment of primary systemic carnitine deficiency. In the reported cases, the clinical presentation consisted of recurrent episodes of fatty liver encephalopathy, hypothetic hypoglycemia, and cardiomyopathy. Associated symptoms included hypokalemia, muscle weakness and failure to thrive. A diagnosis of primary carnitine deficiency requires that serum, red cell and tissue carnitine levels be low and that the patient does not have a primary defect in fatty acid or organic acid oxidation (see Clinical Pharmacology). Controlled trials were not conducted, but in some patients, particularly those presenting with cardiomyopathy, carnitine supplementation rapidly alleviated signs and symptoms. Treatment should include, in addition to carnitine, supportive and other therapy as indicated by the condition of the patient.

Contraindications
None known.

Warnings
None known.

Precautions
General
CARNITOR® (Levcarnitine) Oral Solution is for oral/external use only. Not for parenteral use.

Gastrointestinal reactions may result from too rapid consumption of carnitine. CARNITOR® (Levcarnitine) Oral Solution may be consumed alone, or drizzled in drinks or other liquid foods to reduce taste fatigue. It should be consumed slowly and doses should be spaced evenly throughout the day to maximize tolerance.

Carcinogenicity, mutagenesis, impairment of fertility
Mutagenicity tests have been performed in Salmonella typhimurium, Saccharomyces carlsbergensis and Salmonasaccharomyceticum ponids that do not indicate that CARNITOR® (Levcarnitine) is mutagenic.

Long-term animal studies have not been evaluated to evaluate the carcinogenicity of the compound.

Usage in pregnancy
Pregnancy Category B Reproductive studies have been performed in rats and rabbits using parental administration at doses equal or greater than 50 mg/kg/day as the expected oral adult dosage and have revealed no harm to the fetus due to CARNITOR® (Levcarnitine). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers
Levcarnitine is a normal component of human milk. Levcarnitine supplementation in nursing mothers has not been studied.

Pediatric use
See Dosage and Administration

Adverse reactions
Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or DL-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild episodes has been reported only in uricemic patients receiving DL-carnitine. Gastrointestinal adverse reactions with CARNITOR® (Levcarnitine) Oral Solution disinhibited in liquids might be avoided by a 4 L/min infusion, or rate of 20 drops per minute. In general, decrease in the concentration of the infusate or discontinuation of the infusion may eliminate the symptoms. Gastrointestinal adverse reactions or eliminates drug-related patient body odor or gastrointestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration, and after any dosage increases.

Overdosage
There have been no reports of toxicity from carnitine overdose. The oral LD50 of levcarnitine in mice is 19.5 g/kg. Carnitine may cause diarrhea. Overdose should be treated with supportive care.

Dosage and administration
CARNITOR® (Levcarnitine) Tablets:

Adults: The recommended oral dosage for adults is 100 mg two or three times a day using the 330 mg tablets, depending on clinical response.

Infants and children: The recommended oral dosage for infants and children is between 50 and 100 mg/lyte in divided doses, with a maximum of 3 g/day. Dosage should begin at 10 mg/kg/day. The exact dosage will depend on clinical response.

Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations and overall clinical condition.

CARNITOR® (Levcarnitine) Oral Solution:

For oral use only. Not for parenteral use.

Adults: The recommended dosage of levcarnitine is 1 to 3 g/day for a 50 kg subject which is equivalent to 10 to 30 mL/day of CARNITOR® (Levcarnitine) Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 1 g/day, (10 mL/day), and be increased slowly while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Infants and children: The recommended dosage of levcarnitine is 50 to 100 mg/kg/day which is equivalent to 0.5 mL/lyte AGATI CARNITOR® (Levcarnitine) Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 0.5 mL/kg/day, and be increased slowly while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

CARNITOR® (Levcarnitine) Oral Solution may be consumed alone or dissolved in drinks or other liquid foods. Doses should be spaced evenly throughout the day (every 4 to 8 hours) preferably during or following meals and should be consumed slowly in order to minimize taste.

How supplied
CARNITOR® (Levcarnitine) Tablets are supplied as 330 mg, individually foil wrapped tablets in boxes of 90 (NDC 54426-144-07). Store at room temperature (25°C/77°F).

CARNITOR® (Levcarnitine) Oral Solution is supplied in 118 mL (4 oz.) multiple-unit plastic containers. The multiple-unit containers are packaged 24 per case (NDC 54426-145-08). Store at room temperature (25°C/77°F).

Caution
Federal (U.S.A) law prohibits dispensing without prescription.


References
Carnitor®
(Levocarnitine Oral Solution)

Contains L-carnitine 1 gm/10 mL, sucrose syrup; D-L-malic acid. Methyparaben NF; Propylparaben NF; red colors and artificial cherry flavor.

Manufactured by
SIGMA-TAU PHARMACEUTICALS, INC.
200 Orchard Ridge Drive
Cuthbertson, MO 60678

by Barr-National, Inc.
7206 Windsor Boulevard
Baltimore, MD 21207-5642
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

CHEMISTRY REVIEW(S)
CHEMIST'S REVIEW

1. ORGANIZATION 2. NDA NUMBER
IMREDP, HPD-510 18-948

3. NAME AND ADDRESS OF APPLICANT
Sigma-Tau Pharmaceuticals, Inc.
200 Ochard ridge Drive
Gaithersburg, Maryland 20878

4. SUPPLEMENTS/NUMBER, DATE
Supplement S-016 6/30/92

5. NAME OF THE DRUG
Carnitor Tablets and Oral Solution

6. NONPROPRIETARY NAME
Levcarnitine

8. SUPPLEMENT PROVIDES FOR:
Sigma-Tau's Carnitor

9. AMENDMENTS/REPORTS, DATE

10. PHARMACOLOGICAL CATEGORY
Treatment of carnitine deficiency

11. HOW DISPENSED
Oral

12. RELATED IND/NDA/IMF

13. DOSAGE FORM
Tablets and Oral Solution

14. POTENCY
330 mg, 1g/10mL

15. CHEMICAL NAME AND STRUCTURE
C7H15NO3, Mol. Wt. 161.2
α-Hydroxy-γ-trimethylamino butyric acid

16. COMMENTS

17. CONCLUSIONS AND RECOMMENDATIONS
Information provided are satisfactory. The supplement should be approved.
Issue approval letter without delay.

18. NAME REVIEWER SIGNATURE DATE COMPLETED
Dau-Gong Wu, Ph.D. /S/ 7/10/92

FILE NAME: 18948.a16
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

CORRESPONDENCE
June 30, 1992

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: DOCUMENT CONTROL ROOM 14B03
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 18-948
Supplement: Relabel of Levocarnitine Oral Solution (Expedited Review)

Dear Dr. Sobel:

Please refer to our New Drug Application (NDA) for Carnitor® (levocarnitine) Tablets and Oral Solution submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
In connection with Sigma-Tau

The supplement provides for

During a meeting (February 27, 1992) at the Parklawn Building, Mr. Helmut Nunn, Sigma-Tau Representative, discussed with Dr. Y.Y. Chiu and Dr. Duu-Gong Wu. Dr. Chiu was informed of the urgency of the review because the lot in question was going to expire at the end of February 1993. Dr. Chiu agreed to an expedited review.
Enclosed are 12 copies of the final printed over-lay labels and twelve cartons with the printed lot number and expiration date. We also enclose twelve copies of the currently approved bottle labels and package insert. There are no changes in the text.

Respectfully,

Edward D. Helton, Ph.D.
Director, Research and Regulatory Affairs

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encls.