DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

A.C. Hanzas
Director, Regulatory Affairs
Sigma-Tau Pharmaceuticals, Inc.
800 South Frederick Avenue
Gaithersburg, MD 20877

JAN 24 2000

RE: NDA# 20-182
Carnitor (levocarnitine) Injection
ADMIS ID# 92186

Dear Mr. Hanzas:

Reference is made to your December 22, 1999, submission under cover of Form FDA 2253 of a press release regarding Carnitor Injection. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the material and has concluded that it is false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

Specifically, we object to the lack of fair balance because there is no information provided regarding side effects. Risk information should be provided with a prominence and readability reasonably comparable with information regarding effectiveness.

In the event that Sigma-Tau is still disseminating this press release by any means, it should cease immediately. In addition, DDMAC reminds Sigma-Tau that all future press releases for any prescription drug products should provide fairly balanced information. Your response to this letter should include your proposed method for discontinuing the use of this and similar materials. It should be received by this office no later than ten days from the receipt of this letter. It should be directed to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to ADMIS ID #92186 in addition to the NDA number.

Sincerely,

/S/

Margaret M. Kober, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

For Immediate Release

Sigma-Tau Granted Approval for Carnitor® (levocarnitine) Injection in Dialysis

GAITHERSBURG, MD. -- December 22, 1999 -- Sigma-Tau Pharmaceuticals, Inc., the only supplier of prescription form carnitine, announced that it received approval on December 15, 1999 from the U.S. Food and Drug Administration (FDA) to market Carnitor Injection for the prevention and treatment of carnitine deficiency in patients with end stage renal disease (ESRD) who are undergoing dialysis. This indication applies only to the intravenous formulation of Carnitor and not the available oral formulations. This approval comes ten months after Sigma-Tau submitted a supplemental new drug application for Carnitor I.V. in this indication.

Approximately 350,000 Americans are currently living with ESRD, also known as chronic renal failure.

"This approval truly reflects Sigma-Tau's long-standing commitment to patients who have carnitine deficiency," said Ken Mehrling, General Manager, Sigma-Tau Pharmaceuticals, Inc. "It also confirms our commitment to being the worldwide leader in carnitine and metabolic research," said Mehrling.

Carnitine is a naturally-occurring substance that is crucial to the metabolic process that provides energy to the body.

Carnitine deficiency is a condition that results when carnitine is not present in sufficient amounts, which disrupts the metabolic process in which cells turn nutrients into energy. ESRD patients on maintenance hemodialysis may have low plasma carnitine concentrations and an increased ratio of acylcarnitine/carnitine because of reduced intake of meat and dairy products, reduced renal synthesis, and dialytic losses. Certain clinical conditions common in hemodialysis patients such as malaise, muscle weakness, cardiomyopathy and cardiac arrhythmias may be related to abnormal carnitine metabolism.

Pharmacokinetic and clinical studies with intravenous Carnitor have shown that administration of levocarnitine to ESRD patients on hemodialysis results in increased plasma levocarnitine concentrations.

Sigma-Tau, who more than 10 years ago pioneered the development of the only prescription form of carnitine, maintains its leadership in the U.S. market today. In 1989, Carnitor (levocarnitine) tablets and oral solution were approved for the treatment of primary systemic carnitine deficiency. Carnitor Injection was approved in 1992 for the acute and chronic treatment of patients with an inborn error of metabolism which results in secondary carnitine deficiency.

— more —

Carnitor® Injection in Dialysis / Add One

Established in 1980, Sigma-Tau Pharmaceuticals, Inc. is the U.S. subsidiary of Italy's leading research-based pharmaceutical company, Sigma-Tau S.p.A. Sigma-Tau is the worldwide leader in carnitine and metabolic research. Carnitor, Sigma-Tau's flagship product, is the only prescription drug approved in the United States for the treatment of carnitine deficiency. The company has invested significant resources in the development of orphan products that contribute to the health and well-being of humanity. Sigma-Tau is committed to helping ensure that no patient is overlooked.

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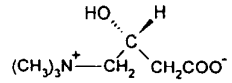
CARNITOR® (levocarnitine)

CARNITOR® (levocarnitine) Injection 1 g per 5 mL and 500 mg per 2.5 mL
FOR INTRAVENOUS USE ONLY.

DESCRIPTION

CARNITOR® (levocarnitine) is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane.

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:



Empirical Formula: $C_7H_{15}NO_3$
Molecular Weight: 161.20

CARNITOR® (levocarnitine) Injection is a sterile aqueous solution containing 1 g of levocarnitine per 5 mL ampoule and 500 mg of levocarnitine per 2.5 mL ampoule. The pH is adjusted to 6.0 - 6.5 with hydrochloric acid.

CLINICAL PHARMACOLOGY

CARNITOR® (levocarnitine) is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, thereby 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, fatty acids are the main substrate for energy production.

Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, RBC, and/or tissues. It has not been possible to determine which symptoms are due to carnitine deficiency and which are due to an underlying organic acidemia, as symptoms of both abnormalities may be expected to improve with CARNITOR®. 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 bioaccumulate acylCoA esters.[1-6]

Secondary carnitine deficiency can be a consequence of inborn errors of metabolism or iatrogenic factors such as hemodialysis. CARNITOR® may alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids. Conditions for which this effect has been demonstrated are: glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency.[7,8] Autointoxication occurs in these patients due to the accumulations of acylCoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acylCoA compound to its free acid results in acidosis which can be life-threatening. Levocarnitine clears the acylCoA compound by formation of acylcarnitine, which is quickly excreted. Carnitine deficiency is defined biochemically as abnormally low plasma concentrations of free carnitine, less than 20 µmol/L at one week post term and may be associated with low tissue 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. In premature infants and newborns, secondary deficiency is defined as plasma levocarnitine concentrations below age-related normal concentrations.

End Stage Renal Disease (ESRD) patients on maintenance hemodialysis may have low plasma carnitine concentrations and an increased ratio of acylcarnitine/carnitine because of reduced intake of meat and dairy products, reduced renal synthesis, and dialytic losses. Certain clinical conditions common in hemodialysis patients as malaise, muscle weakness, cardiomyopathy and cardiac arrhythmias may be related to abnormal carnitine metabolism.

Pharmacokinetic and clinical studies with CARNITOR® have shown that administration of levocarnitine to ESRD patients on hemodialysis results in increased plasma levocarnitine concentrations.

PHARMACOKINETICS

In a relative bioavailability study in 15 healthy adult male volunteers CARNITOR® Tablets were found to be bio-equivalent to CARNITOR® Oral Solution. Following 4 days of dosing with 6 tablets of CARNITOR® 330 mg bid or 2 g of CARNITOR® oral solution bid, the maximum plasma concentration (C_{max}) was about 80 µmol/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 CARNITOR® were described by a two-compartment model. Following a single i.v. administration, approximately 76% of the levocarnitine dose was excreted in the 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 CARNITOR®, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for CARNITOR® Tablets and 15.9 ± 4.9% for CARNITOR® 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]

In a 9-week study, 12 ESRD patients undergoing hemodialysis for at least 6 months received CARNITOR® 20 mg/kg three times per week after dialysis. Prior to initiation of CARNITOR® therapy, mean plasma levocarnitine concentrations were approximately 20 µmol/L pre-dialysis and 6 µmol/L post-dialysis. The table summarizes the pharmacokinetic data (mean ± SD µmol/L) after the first dose of CARNITOR® and after 8 weeks of CARNITOR® therapy.

N=12	Baseline	Single dose	8 weeks
C_{max}	-	1139 ± 240	1190 ± 270
Trough (pre-dialysis, pre-dose)	21.3 ± 7.7	68.4 ± 26.1	190 ± 55

After one week of CARNITOR® therapy (3 doses), all patients had trough concentrations between 54 and 180 µmol/L (normal 40-50 µmol/L) and concentrations remained relatively stable or increased over the course of the study.

In a similar study in ESRD patients also receiving 20 mg/kg CARNITOR® 3 times per week after hemodialysis, 12 and 24-week mean pre-dialysis (trough) levocarnitine concentrations were 189 (N=25) and 243 (N=23) µmol/L, respectively.

In a dose-ranging study in ESRD patients undergoing hemodialysis, patients received 10, 20, or 40 mg/kg CARNITOR® 3 times per week following dialysis (N~30 for each dose group). Mean ± SD trough levocarnitine concentrations (µmol/L) by dose after 12 and 24 weeks of therapy are summarized in the table.

	12 weeks	24 weeks
10 mg/kg	116 ± 69	148 ± 50
20 mg/kg	210 ± 58	240 ± 60
40 mg/kg	371 ± 111	456 ± 162

While the efficacy of CARNITOR® to increase carnitine concentrations in patients with ESRD undergoing dialysis has been demonstrated, the effects of supplemental carnitine on the signs and symptoms of carnitine deficiency and on clinical outcomes in this population have not been determined.

METABOLISM AND EXCRETION

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. Maximum concentration of [^{3}H-methyl]-L-carnitine in serum occurred from 2.0 to 4.5 hr after drug administration. Major metabolites found were trimethylamine N-oxide, primarily in urine (8% to 49% of the administered dose) and [^{3}H]-γ-butyrobetaine, primarily in feces (0.44% to 45% of the administered dose). 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]

After attainment of steady state following 4 days of oral administration of CARNITOR® 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 dosing interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

INDICATIONS AND USAGE

For the acute and chronic treatment of patients with an inborn error of metabolism which results in secondary carnitine deficiency.

For the prevention and treatment of carnitine deficiency in patients with end stage renal disease who are undergoing dialysis.

CONTRAINDICATIONS

None known.

WARNINGS

None.

PRECAUTIONS

Carcinogenesis, mutagenesis, impairment of fertility

Mutagenicity tests performed in *Salmonella typhimurium*, *Saccharomyces cerevisiae*, and *Schizosaccharomyces pombe* indicate that levocarnitine is not mutagenic. No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine.

PREGNANCY

Pregnancy Category B.

Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to CARNITOR®. 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

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.