CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020182, S006

FINAL PRINTED LABELING

12/13/99

APPROVED

DEC 15 1999

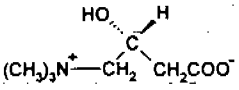
CARNITOR® (levocarnitine)

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.

PEDIATRIC USE

See Dosage and administration.

ADVERSE REACTIONS

Transient nausea and vomiting have been observed. Less frequent adverse reactions are body odor, nausea, and gastritis. An incidence for these reactions is difficult to estimate due to the confounding effects of the underlying pathology.

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, an increase in seizure frequency and/or severity has been reported.

The table below lists the adverse events that have been reported in two double-blind, placebo-controlled trials in patients on chronic hemodialysis. Events occurring at ≥5% are reported without regard to causality.

Adverse Events with a Frequency ≥5% Regardless of Causality by Body System

	Placebo (n=63)	*Levocarnitine 10 mg (n=34)*	*Levocarnitine 20 mg (n=62)*	*Levocarnitine 40 mg (n=34)*	*Levocarnitine 10, 20 & 40 mg (n=130)*
Body as Whole					
Abdominal pain	17	21	5	6	9
Accidental injury	10	12	8	12	10
Allergic reaction	5	6			2
Asthenia	8	9	8	12	9
Back pain	10	9	8	6	8
Chest pain	14	6	15	12	12
Fever	5	6	5	12	7
Flu syndrome	40	15	27	29	25
Headache	16	12	37	3	22
Infection	17	15	10	24	15
Injection site reaction	59	38	27	38	33
Pain	49	21	32	35	30
Cardiovascular					
Arrhythmia	5	3		3	2
Atrial fibrillation			2	6	2
Cardiovascular disorder	6	3	5	6	5
Electrocardiogram abnormal		3		6	2
Hemorrhage	6	9	2	3	4
Hypertension	14	18	21	21	20
Hypotension	19	15	19	3	14
Palpitations		3	8		5
Tachycardia	5	6	5	9	6
Vascular disorder	2		2	6	2
Digestive					
Anorexia	3	3	5	6	5
Constipation	6	3	3	3	3
Diarrhea	19	9	10	35	16
Dyspepsia	10	9	6		5
Gastrointestinal disorder	2	3		6	2
Melena	3	6			2
Nausea	10	9	5	12	8
Stomach atony	5				
Vomiting	16	9	16	21	15

	Placebo (n=63)	Levocarnitine 10 mg (n=34)	Levocarnitine 20 mg (n=62)	Levocarnitine 40 mg (n=34)	Levocarnitine 10, 20 & 40 mg (n=130)
Endocrine System					
Parathyroid disorder	2	6	2	6	4
Hemic/Lymphatic					
Anemia	3	3	5	12	6
Metabolic/ Nutritional					
Hypercalcemia	3	15	8	6	9
Hyperkalemia	6	6	6	6	6
Hypervolemia	17	3	3	12	5
Peripheral edema	3	6	5	3	5
Weight decrease	3	3	8	3	5
Weight increase	2	3		6	2
Musculo-Skeletal					
Leg cramps	13		8		4
Myalgia	6				
Nervous					
Anxiety	5		2		1
Depression	3	6	5	6	5
Dizziness	11	18	10	15	13
Drug dependence	2	6			2
Hypertonia	5	3			1
Insomnia	6	3	6		4
Paresthesia	3	3	3	12	5
Vertigo		6			2
Respiratory					
Bronchitis			5	3	3
Cough increase	16		10	18	9
Dyspnea	19	3	11	3	7
Pharyngitis	33	24	27	15	23
Respiratory disorder	5				
Rhinitis	10	6	11	6	9
Sinusitis	5		2	3	2
Skin And Appendages					
Pruritus	13		8	3	5
Rash	3		5	3	3
Special Senses					
Amblyopia	2		6		3
Eye disorder	3	6	3		3
Taste perversion			2	9	3
Urogenital					
Urinary tract infect	6	3	3		2
Kidney failure	5	6	6	6	6

OVERDOSAGE

There have been no reports of toxicity from levocarnitine overdosage. 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. Large doses of levocarnitine may cause diarrhea.

DOSAGE AND ADMINISTRATION

CARNITOR® Injection is administered intravenously.

Metabolic Disorders

The recommended dose is 50 mg/kg given as a slow 2-3 minute bolus injection or by infusion. Often a loading dose is given in patients with severe metabolic crisis, followed by an equivalent dose over the following 24 hours. It should be administered q3h or q4h, and never less than q6h either by infusion or by intravenous injection. All subsequent daily doses are recommended to be in the range of 50 mg/kg or as therapy may require. The highest dose administered has been 300 mg/kg.

It is recommended that a plasma carnitine concentration be obtained prior to beginning this parenteral therapy. Weekly and monthly monitoring is recommended as well. This monitoring should include blood chemistries, vital signs, plasma carnitine concentrations (the plasma free carnitine concentration should be between 35 and 60 μmol/L) and overall clinical condition.

ESRD Patients on Hemodialysis

The recommended starting dose is 10-20 mg/kg dry body weight as a slow 2-3 minute bolus injection into the venous return line after each dialysis session. Initiation of therapy may be prompted by trough (pre-dialysis) plasma levocarnitine concentrations that are below normal (40-50 μmol/L). Dose adjustments should be guided by trough (pre-dialysis) levocarnitine concentrations, and downward dose adjustments (e.g. to 5 mg/kg after dialysis) may be made as early as the third or fourth week of therapy.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

COMPATIBILITY AND STABILITY

CARNITOR® Injection is compatible and stable when mixed in parenteral solutions of Sodium Chloride 0.9% or Lactated Ringer's in concentrations ranging from 250 mg/500 mL (0.5 mg/mL) to 4200 mg/500 mL (8.0 mg/mL) and stored at room temperature (25°C) for up to 24 hours in PVC plastic bags.

HOW SUPPLIED

CARNITOR® (levocarnitine) Injection is available in 1 g per 5 mL single dose ampoules packaged 5 ampoules per carton (NDC 54482-146-09) or in 500 mg per 2.5 mL single dose ampoules packaged 5 ampoules per carton (NDC 54482-146-10). Made in Italy.

Store ampoules at controlled room temperature (25°C). See USP. Store in carton until their use to protect from light. Discard unused portion of an opened ampoule, as the formulation does not contain a preservative.

CARNITOR® (levocarnitine) is also available in the following dosage forms for oral administration:

CARNITOR® (levocarnitine) Tablets are supplied as 330 mg tablets embossed with "CARNITOR ST" in blister packages, in boxes of 90 tablets (NDC 54482-144-07). Made in Italy.

CARNITOR® (levocarnitine) Oral Solution is supplied in 118 mL (4 FL. OZ.) multiple-unit plastic containers. The multiple-unit containers are packaged 24 per case (NDC 54482-145-08). CARNITOR® (levocarnitine) Oral Solution is manufactured for Sigma-Tau Pharmaceuticals, Inc. by: Alpharma USPD, Inc. Baltimore, MD 21244-2654 and/or Hi-Tech Pharmacal Co., Inc. Amityville, NY 11701.

Rx only.

References

1. Bohmer, T., Rynding, A. and Solberg, H.E. 1974. Carnitine levels in human serum in health and disease. *Clin. Chim. Acta* 57:55-61.
2. Brooks, H., Goldberg, L., Holland, R. *et al.* 1977. Carnitine-induced effects on cardiac and peripheral hemodynamics. *J. Clin. Pharmacol.* 17:561-578.
3. Christiansen, R., Bremer, J. 1977. Active transport of butyrobetaine and carnitine into isolated liver cells. *Biochem. Biophys. Acta* 448:562-577.
4. Lindstedt, S. and Lindstedt, G. 1961. Distribution and excretion of carnitine $^{14}CO2$ in the rat. *Acta Chim. Scand.* 15:701-702.
5. Rebouche, C.J. and Engel, A.G. 1983. Carnitine metabolism and deficiency syndromes. *Mayo Clin. Proc.* 58:533-540.
6. Rebouche, C.J. and Paulson, D.J. 1986. Carnitine metabolism and function in humans. *Ann. Rev. Nutr.* 6:41-68.
7. Scriver, C.R., Beaudet, A.L., Sly, W.S. and Valle, D. 1989. *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill.
8. Schaub, J., Van Hoof, F. and Vis, H.L. 1991. *Inborn Errors of Metabolism*. New York: Raven Press.
9. Marzo, A., Arrigoni Martelli, E., Mancinelli, A., Cardace, G., Corbelletta, C., Bassani, E. and Solbiati, M. 1992. Protein binding of L-carnitine family components. *Eur. J. Drug Met. Pharmacokin.*, Special Issue III: 364-368.
10. Rebouche, C. 1991.Quantitative estimation of absorption and degradation of a carnitine supplement by human adults. *Metabolism* 1305-1310.

533331

sigma-tau s.p.a.
industrie farmaceutiche riunite

Pharmaceuticals, Inc.
Gaithersburg, MD 20877

PREVIOUS EDITION IS OBSOLETE
ST-N20-182-12/99